

**NATIONAL INSTITUTES OF HEALTH
DEPARTMENT OF HEALTH AND HUMAN SERVICES**

**GENERAL CLINICAL RESEARCH CENTERS PROGRAM
DIVISION OF CLINICAL RESEARCH RESOURCES
NATIONAL CENTER FOR RESEARCH RESOURCES**

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GENERAL CLINICAL RESEARCH CENTER

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UNIVERSITY OF CONNECTICUT HEALTH CENTER

SCHOOL OF MEDICINE

ANNUAL PROGRESS REPORT

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Date

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PERSONNEL ROSTER

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Name, Degree	Department	Non-Host Institution: State, Country
ABU-HASABALLAH, KHAMIS, PHD	Psychiatry	
ADAMS, NANCY, MD	Medicine/Nephrology	
AFFLECK, GLENN, PHD	Community Medicine	
AGUILA, LEONARDO, PHD	Medicine	
ALBERT, DAVID, PHD	Psychiatry	
ALBERTSEN, PETER, MD	Surgery	
ALESSI, SHELIA, PHD	Psychiatry	
ALLEN, HOLLY, MD	PEDIATRIC ENDOCRINOLOGY	BAYSTATE MEDICAL CENTER: MA, USA
ARIAS, ALBERT, MD	Psychiatry	
ARMELL, STEPHEN R, PHD	PSYCHIATRY	FAIRLEIGH-DICKINSON UNIV: NJ, USA
ARMSTRONG, AMY, BS	GCRC	
ARNOLD, ANDREW, MD	Medicine	
ASELTINE, ROBERT H, PHD	BEHAVIORAL SCI & COMM HLTH	
ASTUR, ROBERT S, PHD	OLIN CENTER	HARTFORD HOSPITAL: CT, USA
AZIZ, KHALID, MD	Medicine	
BABOR, THOMAS F, PHD	COMMUNITY MEDICINE	
BANDYOPADHYAY, TAPAS, MD	Pulmonary/Medicine	
BARTA, WILLIAM D, PHD	PSYCHOLOGY	UCONN - STORRS: CT, USA
BAUER, LANCE D, PHD	PSYCHIATRY	
BENITEZ, HUBERT, DDS,MHA	Biostructure & Function	
BENMAMOUN, CHOUKRI, MD	Microbial Pathology	
BONA, ROBERT, MD	Medicine/Hem-Onc	
BONKOVSKY, HERBERT L, MD	MEDICINE/GASTROENTEROLOGY	
BOXER, REBECCA, MD	Medicine/Geriatrics	
BURKI, NAUSHERWAN K, MD	Medicine/Pulmonary Medicin	
BURLESON, JOSEPH, PHD	Behavioral Sciences	
CABRAL, CYNTHIA, BS	Dental-Students	
CALHOUN, VINCE D, MD	PSYCHIATRY	YALE UNIVERSITY: CT, USA
CAMPBELL, WINSTON, MD	Obstetrics/Gynecology	
CAPRIGLIONE, ANTOINETTE, MD	OBSTETRICS/GYNECOLOGY	NEW BRITAIN GENERAL HOSPITAL: CT, USA
CARROLL, CHRISTOPHER, MD	PEDIATRICS	CONNECTICUT CHILDREN'S MEDICAL: CT, USA
CARROLL, KATHLEEN M, PHD	MEDICINE	YALE UNIVERSITY: CT, USA
CARTER, WILLIAM, BS	GCRC	
CHAKRABORTY, NITYA G, PHD	Medicine	
CHERNIACK, MARTIN G, MD	OCCUPATIONAL/ENVIRONMENTAL	
CILLESSEN, ANTONIUS, PHD	PSYCHOLOGY	UCONN, STORRS: CT, USA
CLOUTIER, MICHELLE M, MD	PEDIATRICS	
COBB, RICHARD, MD	Diagnostic Imaging	
CONNER, TAMLIN, PHD	Psychiatry	
COONEY, JUDITH, PHD	MEDICINE	YALE UNIVERSITY: CT, USA
COONEY, NED L, PHD	PSYCHIATRY	YALE UNIVERSITY: CT, USA
COVAULT, JONATHAN, MD,PHD	Psychiatry	
CRANFORD, JAMES A, PHD	SUBSTANCE ABUSE RESEARCH	UNIVERSITY OF MICHIGAN: MI, USA
DAMATO, KATHRYN L, MS	Oral Diagnosis	
DANNENBERG, ANDREW J, MD	MEDICINE/GASTROENTEROLOGY	CORNELL UNIVERSITY: NY, USA

DAVENPORT, MARSHA, MD	PEDIATRICS	UNIVERSITY OF NORTH CAROLINA: NC, USA
DECKERS, PETER, MD	Surgery	
DEHART, TRACY, PHD	PSYCHOLOGY	LOYOLA UNIV: IL, USA
DEMARTINIS, NICHOLAS, MD	Psychiatry	
DIECKHAUS, KEVIN, MD	Medicine/Infectious Diseases	
DIPASQUALE, CHRIS, PHD	KINESIOLOGY	UCONN - STORRS: CT, USA
DONGARI-BAGTZOGLOU, ANNA I, DDS,PHD	PERIODONTOLOGY	
DOWSETT, ROBERT J, MD	Radiation Oncology	
DRAZINIC, CAROLYN, MD	Psychiatry	
DUFFY, VALERIE, PHD	ALLIED HEALTH SCIENCES	UCONN, STORRS: CT, USA
ELSHEIKHA, HANY, PHD	MICROBIOLOGY	
ESAYAG-TENDLER, BEATRICE, MD	Medicine	
ESTRADA, ELIZABETH, MD	PEDIATRICS	CONNECTICUT CHILDREN'S MEDICAL: CT, USA
FANG, MIN, MD,PHD	Genetics & Dev. Biology	
FEDER, HENRY, MD	Medicine/Family Medicine	
FELICE, KEVIN, DO	Medicine/Neurology	
FISHER, JEFFREY D, PHD	PSYCHOLOGY	UCONN - STORRS: CT, USA
FORD, JULIAN D, PHD	PSYCHIATRY	
FORMAKER, BRADLEY, PHD	Oral Health & Diagnostics	
FORTINSKY, RICHARD H, BA	CENTER ON AGING	
FRANK, MARION E, DMD	ORAL DIAGNOSIS	
FREILICH, MARTIN A, DDS	Prosthodontics	
FRESTON, JAMES, MD	Medicine	
FRIEDLAND, GERALD H, MD	MEDICINE/EPIDEMIOLOGY	YALE UNIVERSITY: CT, USA
FURNEAUX, HENRY M, PHD	VASCULAR BIOLOGY	
GELERNTER, JOEL E, MD	PSYCHIATRY	YALE UNIVERSITY: CT, USA
GOLDBERG, JON, PHD	Biomaterials	
GRAVELEY, BRENTON R, PHD	GENETICS AND DEV BIOLOGY	
GREENSTEIN, ROBERT, MD	Pediatrics/Genetics	
GUNTHER, KATHLEEN, PHD	PSYCHOLOGY	AMERICAN UNIVERSITY: DC, USA
GUTMAN, CHARLES, MD	CNTR FOR NEUROLOGICAL IMG	BRIGHAM & WOMENS HOSPITAL: MA, USA
HAGER, DAVID, MD	Medicine/Cardio-Pulmonary	
HEGDE, UPENDRA, MD	Medicine	
HERBST, SARAH, BS	GCRC	
HERMAN, AREY, BA	Psychiatry	
HERNANDEZ-AVILA, CARLOS, MD	Psychiatry	
HESELBROCK, VICTOR M, PHD	PSYCHIATRY	
HETTINGER, THOMAS, PHD	Oral Health & Diagnostic	
HLA, TIMOTHY T, PHD	CELL BIOLOGY	
HULL, DAVID, MD	SURGERY	HARTFORD HOSPITAL: CT, USA
HUSSAIN, NAVEED, MD	Pediatrics	
IOANNIDOU, EFFIE, DDS	Periodontology	
ISAKOFF, MICHAEL, MD	PEDIATRICS	CONNECTICUT CHILDREN'S MEDICAL CENTER: CT, USA
JAMES, AMY, PHD	Behavioral Sci & Comm Hlth	
JENSEN, KEVIN, BS	VASCULAR BIOLOGY	
JOSEPH, CHERIAN, MD	Medicine/Geriatrics	
KADDEN, RONALD M, PHD	Psychiatry	
KAMINER, YIFRAH, PHD	Psychiatry	
KAPLAN, RICHARD, PHD	Psychiatry	
KELLY, JOHN R, DDS,DSC	Oral Rehab, Biomaterials	

KENNY, ANNE M, MD	CENTER ON AGING	
KERSTETTER, JANE, PHD	NUTRITIONAL SCIENCE	UCONN - STORRS: CT, USA
KING, ANDREA C, PHD	DEPT OF PSYCHIATRY	UNIVERSITY OF CHICAGO: IL, USA
KINGSBURY, JEFFREY, DDS,MD	Oral & Maxillofacial Surge	
KNOX, ISABELLA, MD	Pediatrics	
KRANZLER, HENRY R, MD	PSYCHIATRY	
KRAUSE, PETER, MD	Pediatrics	
KREUTZER, DONALD L, PHD	Pathology	
KUCHEL, GEORGE A, MD	CENTER ON AGING	
KURTZMAN, SCOTT, MD	Surgery	
LALANDE, MARC, MD	Genetics & Develop Biology	
LALLA, RAJESH V, BDS,PHD	ORAL DIAGNOSIS	
LAMBRECHT, RICHARD, PHD	Pharmacology & Toxicology	
LAMMI, KEEFE, PHD	NUTRITIONAL SCIENCE	UCONN, STORRS: CT, USA
LAPIN, CRAIG, MD	Pediatrics	
LEGER, ROBIN, PHD,RN	Orthopedics	
LEWIS, COURTLAND, MD	Orthopedics	
LI, ZIHAI, MD,PHD	Ctr for Immunotherapy	
LILLO, ALYSSA, BS	GCRC	
LITT, MARK D, PHD	BEHAVIORAL SCI & COMM HLTH	
LORENZO, JOSEPH A, MD	MEDICINE	
MALCHOFF, CARL, MD,PHD	Medicine/Endocrinology	
MALCHOFF, DIANA, PHD	Medicine	
MANSOOR, GEORGE, MD	Medicine/Hypertension	
MARKS, LAWRENCE E, PHD	GENERAL MEDICINE	PIERCE FOUNDATION LABORATORY: CT, USA
MARTIN, ISHMAEL, MD	Pulmonary	
MAYER, BRUCE J, PHD	GENETICS & DEV BIOLOGY	
MCELHANEY, JANET E, MD	IMMUNOLOGY	
MEIERS, JONATHAN, DDS	Prosthodontics	
MEYER, JOHN D, MD,PHD	OCCUPATIONAL MEDICINE	
MIRZA, FARYAL, MD	Medicine	
MODESTO, VANIA, MD	Psychiatry	
MOFFITT, KATHIE H, PHD	Psychiatry	
MOHLER, WILLIAM A, PHD	GENETICS & DEV BIOLOGY	
MORRIS, BRUCE, MD	Medicine/Maternal Fetal	
MOYO, VICTOR, MD	Medicine/Oncology	
MUKHERJI, BIJAY, MD	Medicine	
NELLISSERY, MAGGIE, MD	Psychiatry	
NICHOLS, GINGER, MS	Human Genetics	
O'CAMPO, PATRICIA, PHD	MATERNAL/CHILD HEALTH	U OF TORONTO, CANADA
ONCKEN, CHERYL, MD	Medicine	
PACHTER, LEE M, MD	PEDIATRICS	CONNECTICUT CHILDREN'S MEDICAL CENTER: CT, USA
PANZER, VICTORIA, MD	Neurology	
PAPPAGALLO, MARIANN, MD	Pediatrics	
PEARLSON, GODFREY D, MD	PSYCHIATRY	INSTITUTE OF LIVING: CT, USA
PENDRYS, DAVID, DDS,PHD	Behavioral Sci & Comm Hlth	
PERDRIZET, GEORGE, MD,PHD	TRAUMA	HARTFORD HOSPITAL: CT, USA
PETERSON, DOUGLAS, DMD,PHD	Oral Diagnostics	
PETRY, NANCY M, PHD	PSYCHIATRY	
PHULWANI, PRIYA, MD	MEDICINE/ENDOCRINOLOGY	CONNECTICUT CHILDREN'S MEDICAL: CT, USA
PIERUCCI, AMIRA, PHD	Psychiatry	
PILBEAM, CAROL C, MD,PHD	MEDICINE	

PINTO, PAMELA, MD	Medicine	
PRESTWOOD, KAREN, MD	Medicine	
PROTIVA, PETR, MD	Colon Cancer Prevention	
RADOLF, JUSTIN D, MD	MICROBIAL PATHOGENESIS	
RAISZ, LAWRENCE G, MD	Medicine/Endocrinology	
RAJAN, THIRUCHANDURAI V, MD,PHD	Pathology	
REICHENBERGER, ERNST, PHD	Biostructure and Function	
REYNOLDS, JENNIFER, MD	Center for Microbial Patho	
REZAIE, TAYEBEH, PHD	Surgery	
ROSENKRANTZ, TED S, MD	Pediatrics	
ROSSOMANDO, EDWARD F, DDS,MS,PHD	Biostructure & Function	
ROSSON, ROBERT, MD	Medicine	
ROUNSAVILLE, BRUCE J, MD	PSYCHIATRY	YALE UNIVERSITY: CT, USA
RUBIN, KAREN, MD	PEDIATRICS	CONNECTICUT CHILDREN'S MEDICAL: CT, USA
SALAZAR, JUAN C, MD	PEDIATRICS	
SALERMO, EDWARD, MD	Medicine/Pulmonary	
SANDERS, MARILYN, MD	Pediatrics	
SARFARAZI, MANSOOR, PHD	Surgery	
SCHENSUL, JEAN, PHD	INST FOR COMM RESEARCH	UCONN - STORRS: CT, USA
SCHRAMM, CRAIG, MD	Pediatric Pulmonary	
SCOTT, DENISE, BS	GENETICS	HOWARD UNIVERSITY: DC, USA
SECOR, ERIC R, MD	IMMUNOLOGY	
SEIP, RICHARD, PHD	PREVENTIVE CARDIOLOGY	HARTFORD HOSPITAL: CT, USA
SHAFFER, DAVID, DMD	Behavioral Sci & Comm Hlth	
SHARMA, PRIYA, BS	GCRC	
SILVERMAN, DAVID I, MD	Medicine	
SMARADOTTIR, AGNES, MD	Medicine/Hem-Onc	
SMITH, JOANNE, MD	Medicine	
SONIS, STEPHEN T, DMD,DMSC	ORAL & MAXILLOFACIAL SURGE	DANA FARBER CANCER INSTITUTE: MA, USA
SPENCER, TAYLOR, BS	Medicine	
SPIELMAN, ANDREW, SCD	TROPICAL PUBLIC HEALTH	HARVARD UNIVERSITY: MA, USA
SPIRO, JEFFREY, MD	Surgery	
SPORN, JONATHAN, MD	CANCER CENTER	ST. FRANCIS HOSPITAL: CT, USA
SQUIER, RACHEL, DMD,DSC	Prosthodontics	
SRIVASTAVA, PRAMOD K, PHD	IMMUNOLOGY	
STEINBERG, KAREN L, PHD	PSYCHIATRY	
STEVENS, MICHAEL C, PHD	OLIN CENTER	HARTFORD HOSPITAL: CT, USA
SULLIVAN, TAMI P, PHD	FAMILY VIOLENCE RESEARCH A	YALE UNIVERSITY: CT, USA
TANEV, KALOYAN, MD	Psychiatry	
TANNENBAUM, SUSAN, MD	Medicine/Hem-Onc	
TAXEL, PAMELA, MD	Medicine	
TAYLOR, ROBERT E, MD	PHARMACOLOGY	HOWARD UNIVERSITY: DC, USA
TELFORD, SAM R, SCD	INFECTIOUS DISEASE/IMMUNOL	TUFTS UNIVERSITY: MA, USA
TENNEN, HOWARD, PHD	Community Medicine	
THAPAR, MANISH, MD	Internal Medicine	
THOMPSON, PAUL, MD	PREVENTIVE CARDIOLOGY	HARTFORD HOSPITAL: CT, USA
THRALL, ROGER S, PHD	MEDICINE/PULMONARY	
TRAPE, MARCIA, MD	Occupational Medicine	
TROJIAN, THOMAS, MD	MEDICINE/FAMILY MEDICINE	ST. FRANCIS HOSPITAL: CT, USA
TURNER, GARY, MD	OBSTETRICS/GYNECOLOGY	NEW BRITAIN GENERAL HOSPITAL: CT, USA

VIDWANS, ANIRUDDHA, MD	Pediatrics	
WAGNER, JULIE, PHD	Behavioral Sci & Comm Hlth	
WALSH, STEPHEN J, SCD	Ctr for Biostatistics	
WARFIELD, SIMON K, PHD	RADIOLOGY	BRIGHAM & WOMEN'S HOSPITAL: MA, USA
WARREN, NICHOLAS, PHD	Occupational Medicine	
WATSON, KEVIN, MD	Pulmonary/Medicine	
WAYNIK, ILANA, MD	Pediatrics	
WEINER, SCOTT, MD	PEDIATRICS	NEW BRITAIN GENERAL HOSPITAL: CT, USA
WHALEN, GILES F, MD	Surgery	
WHITAKER, CHARLES, MD	Medicine/Neurology	
WHITE, WILLIAM, MD	Medicine/Hypertension	
WIKEL, STEPHEN, PHD	Microbial Pathogenesis	
WILLIAMS, CARLA, PHD	MEDICINE	HOWARD UNIVERSITY: DC, USA
WINOKUR, ANDREW, MD	Psychiatry	
WOLFSON, LESLIE, MD	Medicine/Neurology	
YIGIT, SEVKET, MD	PEDIATRICS	CONNECTICUT CHILDREN'S MEDICAL: CT, USA
ZABLOTSKY, ALEXANDER, BS	GCRC	
ZARFOS, KRISTEN, MD	Surgery	
ZUCKER, AARON, MD	PEDIATRICS	CONNECTICUT CHILDREN'S MEDICAL: CT, USA

SUBPROJECT DESCRIPTIONS

SPID:	0051	PROTOCOL:	51	TYPE:	RESEARCH	
SHORT TITLE:	COGA					
LONG TITLE:	Collaborative Study on the Genetics of Alcoholism					
AIDS:	N	TOTALS		A	B	D
		Inpatient		0	0	0
START DATE:	9/1/1993	Scatter Bed		0	0	0
Total # pts expected for entire study:	3,175	Outpatient		109	0	0
		Scatter RN Hours		0	0	0
		Offsite Visits		0	0	0
RESEARCH BIONUTRITION	N	MULTICENTER STUDY		Y		
INFORMATICS CORE	N	CLINICAL TRIAL		N		
BIostatistician	N	CORE LAB		Y		
ANCILLARIES ONLY	N					

INVESTIGATOR	DEPARTMENT	NON-HOST INSTITUTION: STATE, COUNTRY
HESSELBROCK, VICTOR M PHD	PSYCHIATRY	
BAUER, LANCE D PHD	PSYCHIATRY	

SUBPROJECT DESCRIPTION:

The primary goal of the Collaborative Study on the Genetics of Alcoholism (COGA) is the elucidation of the genes responsible for susceptibility to alcohol dependence. The COGA project, initiated in 1987, is a large scale family study of alcoholism being conducted at six sites nationwide. The initial clinical assessment has been completed on over 1800 probands and their biological relatives (total N= 12,800) and a five-year follow-up is underway.

SUBPROJECT PROGRESS:

This report covers the period from July 1, 2006 to May 11, 2007 for the COGA Participating Center at the University of Connecticut School of Medicine, Department of Psychiatry. This report covers the period of time devoted to completing activities related to data collection and phenotyping/data analyses. a. Specific Aims for the current grant period include: To identify additional susceptibility and protective genes for alcohol dependence and related phenotypes within regions that provides evidence for linkage. • To localize regions of linkage with newly generated, novel intermediate phenotypes related to behavioral impulsivity. • To test in a prospective study of adolescents and young adults whether a variety of genes, including genes currently identified (such as gamma-aminobutyric acid A receptor, alpha 2 (GABRA2) and alcohol dehydrogenase (ADH), contribute to the risk for alcohol dependence and related disorders and predict the onset of psychopathology in adolescents and young adults. • To develop multivariate phenotypes, based upon data collected across domains of data, for use in genetic analyses. • To examine new statistical methods for use in developing typologies of alcohol dependence. • To provide cross-sectional and longitudinal characterization of probands and family members in relation to different phenotypes, including an examination of the stability of diagnoses and phenotype stability over time. b. Data Collection and Phenotyping Studies / Results 1) Personnel - Some staff changes have occurred over the past year. Phlebotomy services continued to be provided by Ms. Pam Ferzacca, who also performs the necessary laboratory/sample preparation work. Backup assistance, when necessary, continues to be provided by staff from the General Clinical Research Center (GCRC) of the School of Medicine. Ms. Carmel Bourgoin provides secretarial support to the project and Ms. Shirley Crall continued as the study's administrative assistant. Data entry and data management duties over the past year remain the responsibility of the research technician's [Amanda Szewczul, Kathryn Hayden, James Plouffe]. During the past year, Ms. Amanda Szewczul and Kathryn Hayden served as the UConn site's interviewers. Ms. Cheryl McCarter was also available on an 'as needed' basis. Each person is fully trained on the Semi-structured Assessment for the Genetics of Alcoholism (SSAGA-II), Child Semi-structured Assessment for the Genetics of Alcoholism (C-SSAGAs), and neuropsychological testing protocols. Amanda Szewczul was the primary SSAGA/C-SSAGA editor, but she relocated to another state and left the project in late December, 2006. A replacement for Ms Szewczul is being recruited and should be in place about June 15, 2007. James Plouffe served as the site's Event Related Potentials (ERP) technician and will continue in that capacity. The research technician to be hired will serve as a backup ERP technician. Dr. Lance Bauer continues as the investigator responsible for the electrophysiological portion of the study protocol. Dr. Victor Hesselbrock continues as the site principal investigator. Michie Hesselbrock, Ph.D. continues on the project part-time to assist with data analyses and other COGA related activities at the UConn COGA site. She is knowledgeable regarding multivariate analyses and assists with the development of conceptual and statistical phenotypes described in the renewal application. Dr. M. Hesselbrock is a Professor at the University of

Connecticut School of Social Work. Christine Ohannessian, Ph.D. is an assistant professor in the Department of Human Development, University of Delaware will continue to assist with the data analysis of the child and adolescent data sets. Her particular interests are in peer relations and family relations as mediators and moderators of the susceptibility for developing alcoholism among offspring at high risk for alcohol use disorders. She will focus on developing structural equation models (SEM) of 'risk' as proposed in the renewal application. Dr. Ohannessian currently is supported by a NIAAA-funded K01 career development award that began Sept 1, 2005; part of her activities involves SEM analyses of the COGA adolescent data sets. 2. The scope of work proposed for FY18 was completed. During the past year, the UConn site devoted much of its efforts to recruitment of 13-22 year old subjects from previously assessed families for a baseline assessment as proposed in the new grant. As in the past, productivity from the UConn site has been very good; with 365 subjects having completed the new assessment battery. Data entry lags somewhat but will be caught up with the recruitment of the new research assistant. As of May 11, 2007, across all three previous waves of data collection, the UConn site had conducted 3078 adult SSAGA wave I-III interviews, 742 child and adolescent interviews, 1723 DNAs, 1515 cell lines, and 1481 ERPs representing 245 families. This sample includes 46.3% males and 53.7% females; 67.92% are Caucasian (no Hispanic), 26.95% are African-American, 3.2% are Hispanic, and 0.5% belong to other ethnic groups, rates similar to the population prevalence rates of the greater Hartford metropolitan area. UConn has contributed 964 biochemistries, 569 neuropsychological test batteries, and 1513 personality tests to the Masterfile (#153). Data entry with respect to the SSAGA, C-SSAGA, and Family History Assessment Module (FHAM) for waves I-III is now complete. 3. Study Findings/Novel Clinical Phenotypes - Specific Aims of the Novel Phenotype component include: 1). To identify and test both conceptual and multivariate phenotypes of alcohol dependence susceptibility among all available offspring (12-25 year olds) in the COGA sample and at regular two year follow-up intervals thereafter. 2). To test and develop models of "Risk" for susceptibility to heavier drinking and alcohol-related problems including alcohol dependence among 12-22 year old COGA subjects. 3.) To provide a cross-sectional and longitudinal phenotypic characterization of alcohol dependence among adult probands and their adult biological family members using the clinical assessment and neurophysiologic data to examine factors related to the onset and maintenance of drinking, recovery from alcohol dependence, and other aspects of the course of illness. During the current year, our efforts have continued to focus on phenotype development in both the adult and in the child/adolescent data sets. Previously we reported linkage and association to the cholinergic muscarinic 2 receptor gene (CHRM2) on chromosome 7 with evoked electroencephalography (EEG) oscillations (Jones et al., 2004), providing evidence that this gene may be involved in human brain dynamics and cognition. In addition, a small number of genetic markers were genotyped in CHRM2 in the Minnesota Twin and Family Study (Comings et al., 2003) and a Dutch family study (Gosso et al., 2006, in press) and both research groups found evidence that this gene may be involved in intelligence. In the COGA sample, we extensively genotyped single nucleotide polymorphisms (SNPs) within and flanking the CHRM2 gene and found evidence of association with multiple SNPs across CHRM2 and Performance IQ, as measured by the Wechsler Adult Intelligence Scale-Revised (WAIS-R). These results remained significant after taking into account alcohol dependence and depression diagnoses in the sample. We also continued our examination of conditions associated with alcohol-related problems. Alcohol dependence is known to increase the risk for suicidal behavior. Ken Connor and colleagues (in press) examined a heuristic model of suicidal behavior to identify variables that distinguished alcohol-dependent individuals who have presumably made, over their lifetime, transitions from non-ideation to ideation (ideation), ideation to planning (planning), planning to attempt (planned attempt), and ideation but not planning to attempt (unplanned attempt). Using the adult alcohol dependent COGA sample, the probability of having made each transition (e.g., to planning), conditioned upon having made an earlier transition (e.g., to ideation) was calculated. Variables that distinguished subjects who made each transition were evaluated using a series of multivariate logistic regressions. Depression- and anxiety disorders were associated in particular with suicidal ideation and planning, female gender was associated with planned- and unplanned suicide attempts, and alcohol-related aggression was associated with unplanned suicide attempt. Among individuals with alcohol dependence, internalizing disorders may confer risk for suicide attempt by promoting suicidal thoughts and plans whereas elevated risk among women may be related to a greater propensity to take suicidal action rather than to think about or plan suicide per se. Aggression may promote unplanned acts of suicide, consistent with a reactive aggression framework. The analysis of clinical phenotypes of African - Americans in the sample has continued in collaboration with Drs. Denise Scott, Robert Taylor and colleagues at Howard University School of Medicine. It is well known that patterns of alcohol use, abuse and dependence are often found to vary widely among ethnic groups. Using information from samples obtained at Howard University, the sequence and progression of alcohol related life events were investigated in this sample of African Americans and compared with findings from the predominantly caucasian COGA sample. The sequence and mean age of appearance of alcohol-related life events were similar for this sample of 224 African-American men and women. Arguments while drinking was the first alcohol related event to emerge at about 20 years of age. Using alcohol in larger amounts than intended developed next, followed by interference with functioning in multiple life areas such as problems with work or school. The onset of alcohol dependence occurred about 26 years of age, and persistent or recurrent physical or psychological problems emerged around age 27 years. The first initiation of seeking help from a health professional occurred at about 31 years of age. While there were similarities in the progression of alcohol related life problems between the African American and the Caucasian samples, the frequency of symptom endorsement for most problems was significantly higher in the Caucasian sample. Two methodological studies have also been conducted. Previous studies have shown that when assessing child psychopathology, parents tend to report more symptoms than children for externalizing disorders such as attention deficit hyperactivity disorder (ADHD), whereas children tend to report more symptoms for internalizing disorders such as major depression. Whether for clinical or research purposes, parents are also frequently asked to report on their children's experiences with alcohol and drugs. This study examined the correspondence between adolescent and parent reports of adolescent substance use and abuse or dependence (Fisher et al., 2006). Adolescents 12 to 17 years old were interviewed using the child version of the Semi-Structured

Assessment for the Genetics of Alcoholism (C-SSAGA); one parent was also interviewed about each adolescent using the parent version of the C-SSAGA. Sensitivities, specificities, and kappa coefficients were calculated to assess parental agreement with adolescent reports of lifetime substance use and DSM-III-R substance abuse or dependence. It was found that parents are somewhat knowledgeable about their children's use of substances, particularly those that are used most commonly. For example, 55% of adolescents who had smoked cigarettes, 50% who had used alcohol, and 47% who had used marijuana had a parent who knew that they used. However, parents were less aware of substance-related problems experienced by their offspring, agreeing with adolescent reports only 27% of the time for diagnoses of alcohol abuse or dependence and 26% of the time for diagnoses of marijuana abuse or dependence. Parent reports added few cases of substance use for 12 to 13 year-olds and essentially no cases for 16 to 17 year-olds. Parent reports added a nominal number of diagnoses of substance abuse or dependence for older adolescents. In a second study, a review of existing multidimensional empirically derived typologies of alcohol use disorders derived primarily for research purposes was conducted in relation to their clinical utility, including studies using COGA data (Hesselbrock & Hesselbrock, 2006). Studies using multivariate statistical methods for identifying homogeneous groups of subjects were selected for inclusion while theoretically-based typologies were not included. While formal diagnostic criteria typically identify separate categories of alcohol abuse and dependence, several studies using different statistical methods consistently suggest as many as four homogeneous types of alcoholism: a chronic / severe type, a depressed / anxious type, a mildly affected type and an antisocial type. Even though the longitudinal outcomes of few empirically derived subtypes have been examined, alcoholism typologies remain a viable and potentially valuable tool for investigating etiological pathways (and possibly for gene identification), the effectiveness of treatments, and the long-term course of alcohol use disorders. Work has also begun examining several possible intermediate outcomes related to the development of alcohol dependence in both the COGA adult and adolescent samples. Recent literature has suggested that age of initiation of alcohol use, intoxication and binge drinking may be important predictors of alcohol use problems in adolescence and young adulthood.

Adult Binge Drinking and Alcohol Dependence - In the adult SSAGA, there is not a question that directly corresponds to the current definition of "binge drinking", ie 5 or more drinks per occasion etc. Since the SSAGA was initially developed in 1989, it contains the older definition of binge drinking - the question reads "Have you ever gone on binges or bender when you kept on drinking for 2 days or more without sobering up except for sleeping?". It is not the same as asking 'have you ever had 5+ drinks in a 24 hr period'. When this SSAGA question is used from the wave II data set, we find that N=1039 persons with a lifetime DSM-IV diagnosis of alcohol dependence answered this question positively. For 56% of this N=1039, binge drinking first occurred about the same time or after the onset of DSM-IV alcohol dependence. For the 44% (n=457) whose binge drinking preceded the onset of alcohol dependence, 303 (66%) had an onset of alcohol dependence within 5 years of first bingeing and 23% had an onset of alcohol dependence within 10 years of onset of bingeing.

Adolescent Alcohol Use, including Bingeing - About 65% (736/1130) of the COGA teens in wave II have tried alcohol (including a sip), with a wide range of ages for this first experience, ranging from 1 - 17 years old. The modal age of first use is 13, with the median of 12-13 years old. Only 42.5% of the sample (480/1130) have ever had a whole standard drink of alcohol. In the wave II adolescent sample, the C-SSAGA-A did not have a question that specifically asks 'have you ever consumed 5+ drinks in one occasion, etc.' Instead we asked several different questions about what is the largest number of drinks consumed at one time for each grade in school beginning in the sixth grade and going through the 12th grade. The C-SSAGA-A also asked how often this maximum amount was consumed during that year in school. The C-SSAGA-A also asked the adult SSAGA MAX drinks question, a question about how many times that the person had at least 3+ drinks in a 24 hr period and the age at which this first occurred. Since COGA was surveying adolescents as young as 12, setting the bar at 3+ drinks per occasion seemed appropriate. Only 5 twelve year old subjects reported having ever consumed 5+ drinks in a 24 hr period at any time in their life and only 1 reported doing this more than once. The largest number of drinks ever consumed in a 24 hour period and the lifetime frequency of occurrence of this maximum consumption was examined by age. Only 7/278 (2.5%) thirteen year olds reported ever having consumed 5+ drinks in a 24 hr period; of this number, 3 consumed this amount only 1-2 times in their lifetime. Only 17/221 (7.7%) fourteen year olds reported having ever consumed drinking 5+ in a 24hr period. Of this number 11 did so on only 1-2 occasions. At age 15, 60/238 (25%) subjects reported a history of consuming 5+ drinks in a 24 hr period. Of this number, only 11 reported doing so on 1-2 occasions. At age 16, 74/224 (33%) subjects reported a history of consuming 5+ drinks in a 24 hr period. Only 12 reported doing so on one or more occasions. At age 17, 111/219 (51%) subjects reported drinking 5+ drinks in a 24 hr period. Only 7 reported doing so on 1-2 occasions. Thus, the data seem to show that the number of teens binge drinking (5+ drinks in 24 hr period) increases with age across the adolescent years along with the frequency of occasions of binge drinking. An initial analysis indicates that the best predictors of 'binge drinking' are beginning regular alcohol use before age 13 and a history of conduct disorder or oppositional defiant disorder. Parental alcoholism [either one or both parents] does not add to the prediction.

Adolescent Bingeing and Alcohol Dependence - Among the COGA adolescents aged 13-17 years old, alcohol dependence is rare. The prevalence of DSM-III-R alcohol dependence is 5.2% (N=59; 59/1130); DSM-IV alcohol dependence is even more rare with a prevalence rate of 2.5% (28; 28/1130). For those 28 adolescents with a DSM-IV diagnosis of alcohol dependence, 18 (64%) experienced their first binge and the onset of alcohol dependence with one year or less of each other. For the remainder, the time between first binge and onset of alcohol dependence was either 2 yrs (7.1%), 3 yrs (10.7%), 4 years (7.1%) or 5 years (10.7%).

c. Significance The present study provides a fertile database for the identification of clinical and genetic factors related to the risk and development of alcohol dependence. Both association and linkage studies continue to be performed. The influence of age, gender, ethnic/socio-demographic factors, and clinical characteristics on the transmission of alcoholism continue to be examined in this large cross-national database, including an emphasis on externalizing behavior/disinhibition. Further, the database has shown itself to be an excellent resource for studying the development of alcohol-related problems among individuals at high genetic risk for alcohol dependence. A multiwave data set has been obtained on children (ages 7-12 yrs.) and adolescents (ages 13-17 yrs.) at baseline and at five-year intervals. The data collected in waves I-III and

the wave IV data to be collected will provide very fertile databases for the identification of personal, genetic, and environmental factors and their interaction related to the vulnerability for and development of alcohol dependence. The clinical assessment battery to be used in this next wave of data collection has been almost totally automated using computer assisted instrument (CATI) and electronic or web-based methods for data collection. The adolescent and young adult COGA subjects to be assessed in the new grant period have been identified and their assessment continues on schedule, with a good follow-up rate. The follow-up data will provide useful information on the characterization of the disorder over time, including studies of gene-gene interaction and gene - environment interplay. In the coming year, we will continue to examine the influence of certain psychosocial mediator/moderator variables that affect the initiation and maintenance alcohol use in the adolescent sample, with some emphasis on the role of peer and family relations on the initiation of drinking behavior among young adolescents. Genetic association and linkage studies will be performed, using the initial, follow-up, and combined databases. Phenotypes based upon standardized diagnostic systems and novel phenotypes developed from information taken from all aspects of the clinical assessment battery are being used in the search for alcohol dependence susceptibility genes. d. Plans for 2007-2008 1) Personnel - The UConn site anticipates no vacancies in staffing, and a research assistant to replace Amanda Szewczul should be identified by June 15, 2007. No additional personnel changes are anticipated for the coming year. 2) Subject recruitment The UConn site will actively pursue recruiting for the wave IV assessment period. During the current year, UCONN staff have been aggressively locating subjects from the current UCONN sample for this wave of data collection, and many subjects have been scheduled for testing. These efforts are likely to leave the UCONN site on schedule to meet its revised recruitment goals. 3) Phenotyping analyses - In the coming year, an emphasis will continue to be placed on the examination of certain psychosocial mediator/moderator variables that affect alcohol use in the adolescent sample, with some emphasis on the role of peer and family relations on the initiation of drinking behavior among young adolescents [with Drs. Ohannessian and M Hesselbrock]. In addition, genetic association and linkage studies will be performed, using the initial, follow-up, and combined databases with a focus on both qualitative and quantitative externalizing behavior phenotypes. Our initial genetic findings in the adult sample will continue to be examined using more refined phenotypes, with a focus on 'aggression' and conduct problems that reflect behavior resulting from alcohol use as well as behavior that occurs apart from alcohol and other drug use. We will also continue our efforts in relation to examining gene-environment interplay. Specific genes of interest that may have etiological relevance include GABRA2, CHRM2 and the taste receptor gene, TAS16. 4) Human Subjects - There have been no changes in the study protocol since last submission. No subjects have been withdrawn due to untoward consequences of participating in the COGA protocol. In order to comply with the new Health Insurance Portability and Accountability Act (HIPAA) regulations, a HIPAA Authorization form has been developed and put into place and the Informed Consent Form (ICF) modified accordingly. Both the HIPAA Authorization form and the ICF have been approved for use by the UConn Institutional Review Board (IRB), and all UConn site staff and investigators have up-to-date IRB certifications. e. Vertebrate animals - none; Manuscripts in press or under review:

Scott DM, Williams CD, Bland WP, Cain GE, Ferguson CL, Kalu NN, Kwagyan J, Hesselbrock VM, Ehlers CL, and Taylor RE. Clinical course of alcohol dependence in African Americans. *Addictive Behaviors* [under review].

Dick DM, Wang JC, Plunkett J, Aliev F, Hinrichs A, Bertelsen S, Budde JP, Goldstein EL, Kaplan D, Edenberg HJ, Nurnberger, JI Jr., Hesselbrock V, Schuckit MA, Kuperman S, Tischfield J, Porjesz B, Begleiter H, Bierut LJ, & Goate A. Family-based analyses of alcohol dependence yield association with neighboring gene ANKK1 rather than DRD2 [Alcoholism: Clinical & Experimental Research, under review].

Wang JC, Hinrichs AL, Bertelsen S, Kwon JM, Stock H, Budde JP, Dick DM, Bucholz KK, Rice J, Saccone NL, Edenberg H, Hesselbrock V, Kuperman S, Schuckit MA, Bierut LJ, Goate AM. Functional Variants in hTAS2R38 and hTAS2R16 influence alcohol consumption in high-risk families of African American origin. (submitted)
Cavazos-Rehg PA, Spitznagel E, Bucholz KK, Norberg K, Nurnberger JI, Hesselbrock V, Kramer J, Kuperman S, & Bierut LJ. The Relationship between Alcohol Problems and Dependence, Conduct Disorder Symptoms, and Number of Sex Partners in a Sample of Young Adults (submitted).

Stein LAR, Hesselbrock V & Bukstein O. Disruptive Behavior Disorders: Conduct Disorder and Oppositional Defiant Disorder Adolescent Substance Abuse. In : Kaminer Y and Bukstein O (eds), Adolescent Substance Abuse: Co-Morbidity and High Risk. Haworth Press. In press.

Dick DM, Aliev F, Wang JC, Gruzza RA, Schuckit MA, Kuperman S, Kramer J, Hinrichs A, Bertelsen S, Budde JP, Hesselbrock V, Porjesz B, Edenberg H, Bierut LJ, and Goate A. Using dimensional modes of externalizing psychopathology to aid in gene identification. (submitted Archives of General Psychiatry)

Conner KR, Hesselbrock VM, Meldrum SC, Schuckit MA, Bucholz KK, Gamble SA, Wines JD, and Kramer J Transitions to, and Predictors of, Suicidal Ideation, Plans, and Unplanned and Planned Suicide Attempts among 3729 Men and Women with Alcohol Dependence. *Journal of Studies on Alcohol and Drugs* (under review)

Conference presentations: Hesselbrock, V et al. Deviance proneness and alcohol use among young adults - a longitudinal perspective. Presented at the 29th annual meeting of the Research Society on Alcoholism, Baltimore MD, June 26, 2006

Hesselbrock, V et al. Suicide and alcoholism: Common genetic factors? Presented at the International Society for Biomedical Research on Alcoholism, Sydney, Australia, September 11, 2006.

Hesselbrock, V., et al. Phenotypes of alcohol dependence and genetic analyses. Presented at the International Society for Biomedical Research on Alcoholism, Sydney, Australia, September 13, 2006.

Hesselbrock, V & Hesselbrock, M.. Multidimensional subtypes of alcohol dependence. Presented at Alcohol Use Disorders: The Diagnostic Conundrum conference, Newport, Australia, September 14, 2006.

Hesselbrock, V. & Hesselbrock, M. Ethnic and gender comparison of alcohol dependent persons. Presented at Alcohol Use Disorders: The Diagnostic Conundrum conference, Newport, Australia, September 15, 2006.

Hesselbrock V. The Collaborative Study on the Genetics of Alcoholism - It's more than genes! Presented at the annual meeting of the Society for Social Work Research, San Francisco, CA., Jan 13, 2007

Hesselbrock V "Common diagnostic confusions, Addictions, Depression and ASPD - Which is which?", a paper presented as part of a symposium "The "Hidden" Diagnoses in Psychiatry: Implications for Training, Clinical Care, and Outcomes". To be presented at the American Psychiatric Association annual meeting, San Diego, CA, May 23, 2007.

SPID: 0060 **PROTOCOL:** 60 **TYPE:** RESEARCH

SHORT TITLE: Primary Cortisol Resistance

LONG TITLE: Primary Cortisol Resistance

AIDS:	N	TOTALS	A	B	D
		Inpatient	0	0	0
START DATE:	2/27/1998	Scatter Bed	0	0	0
Total # pts expected for entire study:	50	Outpatient	0	0	0
		Scatter RN Hours	0	0	0
		Offsite Visits	0	0	0

RESEARCH BIONUTRITION	N	MULTICENTER STUDY	N
INFORMATICS CORE	N	CLINICAL TRIAL	N
BIostatistician	Y	CORE LAB	N
ANCILLARIES ONLY	N		

INVESTIGATOR	DEPARTMENT	NON-HOST INSTITUTION: STATE, COUNTRY
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MALCHOFF, CARL MD, PHD Medicine/Endocrinology

SUBPROJECT DESCRIPTION:

It is our general hypothesis that primary cortisol resistance is a treatable cause of sexual precocity, hypertension, and in women, hirsutism and menstrual irregularities. There are two specific hypotheses of the studies proposed here. First, we predict that selected clinical, biochemical, and ligand binding measurements are sensitive and specific markers for primary cortisol resistance. Second, we predict that the sexual precocity of primary cortisol resistance can be successfully and safely treated with dexamethasone. Once we understand in detail the clinical and biochemical presentations of this disorder, then we will be able to efficiently screen larger potentially affected populations to determine the frequency of cortisol resistance and to identify potentially treatable individuals.

SUBPROJECT PROGRESS:

There is a total of 19 subjects enrolled since initiation of this study. For the current report period no new subjects have been enrolled. There are no proposed changes in recruitment plans at this time. In addition, there are no unexpected safety concerns concerns to report. There are no proposed changes made or anticipated in the protocol. Manuscripts: D.M. Malchoff and C.D. Malchoff, "Generalized Glucocorticoid Resistance," in Endocrinology, 5th Edition, L.J. DeGroot and J. Jameson, Editors, Elsevier Saunders, 2387-2392, 2006.

SPID: 0074 **PROTOCOL:** 74 **TYPE:** RESEARCH

SHORT TITLE: NSABP P-1 Trial

LONG TITLE: NSABP P-1 A Clinical Trial to Determine the Worth of Tamoxifen for Preventing Breast Cancer

AIDS:	N	TOTALS	A	B	D
		Inpatient	0	0	0
START DATE:	2/28/1993	Scatter Bed	0	0	0
Total # pts expected for entire study:	21	Outpatient	0	0	0
		Scatter RN Hours	0	0	0
		Offsite Visits	0	0	0

RESEARCH BIONUTRITION	N	MULTICENTER STUDY	Y	
INFORMATICS CORE	N	CLINICAL TRIAL	Y	Phase III
BIostatistician	Y	CORE LAB	N	
ANCILLARIES ONLY	N			

INVESTIGATOR	DEPARTMENT	NON-HOST INSTITUTION: STATE, COUNTRY
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KURTZMAN, SCOTT MD	Surgery	
SPORN, JONATHAN MD	CANCER CENTER	ST. FRANCIS HOSPITAL, CT USA

SUBPROJECT DESCRIPTION:

Breast cancer is the most common malignancy affecting women in the US, and the second leading cause of cancer death. We have participated in several National Surgical Adjuvant Breast Project (NSABP) studies. These multi-institutional investigations have examined both prevention (Tamoxifen P-1 Trial) and treatment of breast cancer.

The early results of this prevention study demonstrated a decrease in the incidence of breast cancer of 45% in the group of patients who received tamoxifen. The study results were reported, but not yet published. All participants were informed and are still being followed. The NSABP has not decided how many years these patients will be followed.

SUBPROJECT PROGRESS:

The P-1 study has been officially terminated effective August 10, 2006. There is no further participant contact or Institutional Review Board contact.

SPID: 0094	PROTOCOL: 94	TYPE: RESEARCH
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SHORT TITLE: PACTG 219C

LONG TITLE: Pediatric AIDS Clinical Trial Group (PACTG) 219C: Pediatric Late Outcomes Protocol

AIDS:		TOTALS	A	B	D
	Y	Inpatient	0	0	0
START DATE:	2/3/1994	Scatter Bed	0	0	0
Total # pts expected for entire study:	50	Outpatient	84	0	0
		Scatter RN Hours	0	0	0
		Offsite Visits	0	0	0

RESEARCH BIONUTRITION	N	MULTICENTER STUDY	Y	
INFORMATICS CORE	N	CLINICAL TRIAL	Y	Phase III
BIostatistician	N	CORE LAB	N	
ANCILLARIES ONLY	N			

INVESTIGATOR	DEPARTMENT	NON-HOST INSTITUTION: STATE, COUNTRY
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SALAZAR, JUAN C MD	PEDIATRICS	
FEDER, HENRY MD	Medicine/Family Medicine	
KRAUSE, PETER MD	Pediatrics	

SUBPROJECT DESCRIPTION:

This study is a prospective longitudinal data collection for late outcomes (due to Human Immunodeficiency Virus [HIV] disease progression, treatment effects and/or an interaction of the two) and late treatment effects. The study is open to children who have participated in AIDS Clinical Trial Group (ACTG) treatment trials and infants whose mother participated in ACTG perinatal treatment trials. Data collected included history, physical exam, neurocognitive testing, clinical and laboratory evaluations, morbidity, mortality and quality of life assessments at specific intervals. This is a long-term protocol that allows us to collect clinical data indefinitely.

SUBPROJECT PROGRESS:

The total number of subjects enrolled in the study since initiation is 44 subjects. This protocol was closed to accrual on April 25, 2006 remained open for active patient follow-up. There were 32 active patients being followed for this reporting period. The Study closure plan was announced on Dec 28 2006. The finally study visit deadline was set for March 33, 2007.

There were no unexpected safety concerns in regards to this protocol as per communication in July 2006. The protocol team concluded that there were no unanticipated safety concerns identified from the observational data that was thus far, collected.

SPID: 0161 **PROTOCOL:** 161 **TYPE:** RESEARCH

SHORT TITLE: Molecular Genetics

LONG TITLE: Molecular Genetics and Drug Dependence

AIDS:	N	TOTALS	A	B	D
		Inpatient	0	0	0
START DATE:	7/17/1996	Scatter Bed	0	0	0
Total # pts expected for entire study:	1,200	Outpatient	0	0	0
		Scatter RN Hours	0	0	0
		Offsite Visits	0	0	0

RESEARCH BIONUTRITION	N	MULTICENTER STUDY	N
INFORMATICS CORE	N	CLINICAL TRIAL	N
BIostatistician	Y	CORE LAB	N
ANCILLARIES ONLY	N		

INVESTIGATOR	DEPARTMENT	NON-HOST INSTITUTION: STATE, COUNTRY
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KRANZLER, HENRY R MD PSYCHIATRY

SUBPROJECT DESCRIPTION:

Recent developments in molecular biology have generated increased interest in the genetic basis of a variety of psychiatric disorders, including alcoholism and drug dependence. The goal of this research is to identify and describe genes that have an effect on the alcoholism/drug dependence phenotype(s). We propose to probe the relationship between certain genetic polymorphisms and phenotypes related to alcoholism/drug dependence and to collect a large sample for future family-association studies useful for investigating these relationships. Genetic data will be correlated with other phenotypic data such as personality measures.

SUBPROJECT PROGRESS:

This study is closed to enrollment and has been for more than two years. Data continue to be analyzed and manuscripts published.

SPID: 0177 **PROTOCOL:** 177 **TYPE:** RESEARCH

SHORT TITLE: Naltrexone
LONG TITLE: Targeted Naltrexone for Early Problem Drinkers

AIDS:	N	TOTALS	A	B	D
			Inpatient	0	0
START DATE:	11/25/1996	Scatter Bed	0	0	0
Total # pts expected for entire study:	153	Outpatient	0	0	0
		Scatter RN Hours	0	0	0
		Offsite Visits	0	0	0

RESEARCH BIONUTRITION	N	MULTICENTER STUDY	N
INFORMATICS CORE	N	CLINICAL TRIAL	N
BIostatistician	Y	CORE LAB	N
ANCILLARIES ONLY	N		

INVESTIGATOR	DEPARTMENT	NON-HOST INSTITUTION: STATE, COUNTRY
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KRANZLER, HENRY R MD	PSYCHIATRY	
MODESTO, VANIA MD	Psychiatry	
PIERUCCI, AMIRA PHD	Psychiatry	

SUBPROJECT DESCRIPTION:

Naltrexone, an opioid antagonist, is approved for daily use in patients with alcohol dependence. However, a substantial proportion of the population of the U.S. and many other countries experience problems resulting from their drinking, though they do not meet criteria for alcohol dependence. This placebo-controlled trial compares daily administration of naltrexone with administration that is targeted to the management of high risk drinking situations. Daily diary reporting provides detailed information on life events and mood states and their relation to subjects' desire to drink and alcohol consumption, as well as medication usage.

SUBPROJECT PROGRESS:

Subject enrollment for this clinical trial began in October, 1996 and was completed in March, 2001. A total of 153 subjects were randomized to treatment and the last treatment was delivered on May 8, 2001. Of the subjects randomized, 129 (84%) completed treatment. A total of 141 (92%) subjects were interviewed at endpoint (this includes both subjects who completed the study and those who terminated study participation early), 127 (83%) subjects were interviewed at 3-month follow-up, and 132 (86%) subjects were interviewed at 6-month follow-up. There were no unexpected safety concerns associated with this study. Analysis of the data from this study continues. There have been no new publications associated with this study. One of the two manuscripts mentioned during the annual report last year (the manuscript that was in press" at the time of the last report) was subsequently published (citation: Armeli S, Feinn R, Tennen H, Kranzler HR, "The Effects of Targeted Naltrexone on Alcohol and Affect Reactivity to Daily Interpersonal Events", Experimental and Clinical Psychopharmacology. 2006 May;14(2):199-208). As stated before, the GCRC was cited in this manuscript.

SPID: 0231	PROTOCOL: 231	TYPE: RESEARCH
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SHORT TITLE: Familial Papillary Thyroid Carcinoma

LONG TITLE: Familial Papillary Thyroid Carcinoma

AIDS:	N	TOTALS	A	B	D
		Inpatient	0	0	0
START DATE:	2/27/1998	Scatter Bed	0	0	0
Total # pts expected for entire study:	120	Outpatient	0	0	0
		Scatter RN Hours	0	0	0
		Offsite Visits	0	0	0

RESEARCH BIONUTRITION	N	MULTICENTER STUDY	N
INFORMATICS CORE	N	CLINICAL TRIAL	N
BIostatistician	N	CORE LAB	Y
ANCILLARIES ONLY	N		

INVESTIGATOR	DEPARTMENT	NON-HOST INSTITUTION: STATE, COUNTRY
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MALCHOFF, CARL MD, PHD	Medicine/Endocrinology	
ARNOLD, ANDREW MD	Medicine	
ESAYAG-TENDLER, BEATRICE MD	Medicine	
MALCHOFF, DIANA PHD	Medicine	
SARFARAZI, MANSOOR PHD	Surgery	
WHALEN, GILES F MD	Surgery	

SUBPROJECT DESCRIPTION:

Identification of genes that cause human tumors provides important insight into the mechanisms of tumorigenesis. Inherited malignancies provide an opportunity to identify these pathogenetic genes, since powerful positional cloning methodologies will identify the gene of interest. Because there are relatively few multigeneration familial papillary thyroid carcinoma (fPTC) kindreds, genetic linkage methodologies with positional cloning have not yet been used to investigate fPTC. The purpose of this proposal is to use linkage analysis as the first step in positional cloning of the fPTC susceptibility gene.

SUBPROJECT PROGRESS:

Over the past year 12 new subjects have been enrolled, for a total of 82 subjects in all. No changes in recruitment, no unexpected safety concerns, no new interim data, no changes in protocol.

SPID: 0253 **PROTOCOL:** 253 **TYPE:** RESEARCH

SHORT TITLE: Smoking and Pregnancy - CAP

LONG TITLE: Smoking and Pregnancy - CAP

AIDS:	N	TOTALS	A	B	D
		Inpatient	0	0	0
START DATE:	11/26/1997	Scatter Bed	0	0	0
Total # pts expected for entire study:	100	Outpatient	0	0	0
		Scatter RN Hours	0	0	0
		Offsite Visits	0	0	0

RESEARCH BIONUTRITION	N	MULTICENTER STUDY	N
INFORMATICS CORE	N	CLINICAL TRIAL	N
BIostatistician	Y	CORE LAB	N
ANCILLARIES ONLY	N		

INVESTIGATOR	DEPARTMENT	NON-HOST INSTITUTION: STATE, COUNTRY
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ONCKEN, CHERYL MD	Medicine	
CAMPBELL, WINSTON MD	Obstetrics/Gynecology	
KRANZLER, HENRY R MD	PSYCHIATRY	

SUBPROJECT DESCRIPTION:

The aim of this study is to evaluate the effects of maternal smoking on measures of fetal well-being and to determine whether smoking cessation with nicotine replacement can lessen these effects.

SUBPROJECT PROGRESS:

All subjects have been recruited but none enrolled in the past year. We have just analyzed the data and hope to have a manuscript out this year. We will cite the GCRC.

SPID: 0268	PROTOCOL: 268	TYPE: RESEARCH
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SHORT TITLE:	Complication of Hemophilia and Serum Testing and Storage
LONG TITLE:	Universal Data and Serum Specimen Collection System for Hemophilia.

AIDS:	N	TOTALS	A	B	D
		Inpatient	0	0	0
START DATE:	2/1/1999	Scatter Bed	0	0	0
Total # pts expected for entire study:	90	Outpatient	0	2	0
		Scatter RN Hours	0	0	0
		Offsite Visits	0	0	0

RESEARCH BIONUTRITION	N	MULTICENTER STUDY	N
INFORMATICS CORE	N	CLINICAL TRIAL	N
BIostatistician	N	CORE LAB	Y
ANCILLARIES ONLY	N		

INVESTIGATOR	DEPARTMENT	NON-HOST INSTITUTION: STATE, COUNTRY
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BONA, ROBERT MD	Medicine/Hem-Onc	
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SUBPROJECT DESCRIPTION:

The primary congenital bleeding disorders are hemophilia A and B, which affect approximately 1 in 5,000 males and von Willebrand's Disease which affects 1 in 100 men and women. Several plasma proteins called factors are necessary for normal blood clotting. Persons with hemophilia are either missing a particular factor in their blood that is essential to the clotting process or the protein is present but does not work. Without this factor, bleeding into muscles, joints, and internal organs often occurs without any noticeable trauma. The treatment of a bleeding episode involves the replacement of the missing protein through intravenous administration of factor concentrate which is derived from, or contains components of human blood. The frequent bleeding and the necessary intravenous administration of blood products to control the bleeding are responsible for the two most severe complications of hemophilia: 1) development of chronic joint disease from repeated bleeding into major joints; and 2) infection with viral, blood-borne disease such as hepatitis and human immunodeficiency virus (HIV).

About three-fourths of all persons with hemophilia in the US receive some of their treatment from federally-sponsored, specialized hemophilia treatment centers (HTCs). The Center for Disease Control and Prevention (CDC) provides support to these treatment centers for programs designed to prevent complications of hemophilia.

The Universal Data and Serum Specimen Collection System will extend CDC's collaboration with the HTCs by assisting with the analysis of a uniform set of clinical data which are used to monitor the extent of complications in congenital bleeding disorders in the US. Specific measurements will be used to evaluate the degree of joint disease. In addition, serum will be tested for the presence of blood borne pathogens. The remainder of each serum specimen will be used by the CDC to establish a serum bank for possible future use in evaluating the safety of blood products. Information from this system will be used to assess the safety of the blood supply and to develop and monitor the effectiveness of interventions designed to address the mandate from congress which is to reduce or prevent the complications of hemophilia.

SUBPROJECT PROGRESS:

Number of subjects enrolling during the report period and since initiation of the study: During the above report period, (1) one new study subject was enrolled as a participant, (2) one pediatric study patient had an annual follow-up visit and (3) 4 adult study subjects had an annual follow-up visit.

For Connecticut Children's Medical Center (CCMC) study participants: GCRC processes the blood specimens and sends out the specimens. For adult patients: GCRC will draw the blood specimens, process the specimens and send them to the study site laboratory. Study subjects are enrolled as participants or refusals. The study is being conducted at the University of Connecticut Health Center and CCMC. When the patients/subjects come in for a scheduled visits, they are invited to participate in the study. If a patient is already in the study, they are invited to continue to participate or refuse to participate in the study at their annual visit. - Any changes in recruitment plans that might be needed: None - Unexpected safety concerns and their resolution: None - Interim data and outcomes if appropriate: The study is ongoing. - Any proposed changes made or anticipated in the protocol. None at this time. The current protocol is 8/24/05 - Publications, indicating whether the GCRC was cited: None

SPID: 0279 **PROTOCOL:** 279 **TYPE:** RESEARCH

SHORT TITLE: NSABP Treatment B21

LONG TITLE: NSABP B21 Node Negative Clinical Occult Breast Cancer - Tamoxifen/Radiation

AIDS:	N	TOTALS	A	B	D
		Inpatient	0	0	0
START DATE:	10/1/1989	Scatter Bed	0	0	0
Total # pts expected for entire study:	10	Outpatient	0	1	0
		Scatter RN Hours	0	0	0
		Offsite Visits	0	0	0

RESEARCH BIONUTRITION	N	MULTICENTER STUDY	Y	
INFORMATICS CORE	N	CLINICAL TRIAL	Y	Phase III
BIostatistician	Y	CORE LAB	N	
ANCILLARIES ONLY	N			

INVESTIGATOR	DEPARTMENT	NON-HOST INSTITUTION: STATE, COUNTRY
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KURTZMAN, SCOTT MD Surgery

SUBPROJECT DESCRIPTION:

Patients eligible for this study must have had a lumpectomy with tumor-free specimen margins and axillary node dissection with pathologically-negative axillary nodes. The largest tumor diameter, by pathological examination of the resected specimen, must be < 1 cm. If the pathologic tumor size is indeterminable from the report, then the maximum clinical and mammographic tumor sizes must both be < 1 cm. If a tumor pathologically consists of both an invasive component and an intraductal component, then the maximum diameter of both components when measured together must be < 1 cm. Finally, patients are eligible if a carcinoma pathologically < 1 cm in size is detected in association with a benign lesion of any size. Patients in this study will be randomly assigned to one of three groups: lumpectomy and breast radiation plus placebo, lumpectomy and breast radiation plus tamoxifen, or lumpectomy, tamoxifen and no breast radiation.

SUBPROJECT PROGRESS:

We have enrolled 2 patients into this study and both are without disease and doing well. This study is closed to accrual therefore there is no recruitment plan and there will be no changes made to the protocol. There were no unexpected safety concerns. There are no publications that have cited the GCRC. This study is being terminated.

SPID: 0282 **PROTOCOL:** 282 **TYPE:** RESEARCH

SHORT TITLE: NSABP BI-65 NSABP BI-65

LONG TITLE: NSABP BI-65 Menstrual Cycle in Surgical Treatment of Breast Cancer

AIDS:	N	TOTALS	A	B	D
		Inpatient	0	0	0
START DATE:	9/4/1998	Scatter Bed	0	0	0
Total # pts expected for entire study:	10	Outpatient	0	0	0
		Scatter RN Hours	0	0	0
		Offsite Visits	0	0	0

RESEARCH BIONUTRITION	N	MULTICENTER STUDY	Y	
INFORMATICS CORE	N	CLINICAL TRIAL	Y	Phase III
BIostatistician	Y	CORE LAB	N	
ANCILLARIES ONLY	N			

INVESTIGATOR	DEPARTMENT	NON-HOST INSTITUTION: STATE, COUNTRY
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KURTZMAN, SCOTT MD Surgery

SUBPROJECT DESCRIPTION:

The purpose of this study is to evaluate whether the timing of breast cancer surgery during a woman's menstrual cycle affects her ultimate outcome- namely, the likelihood of recurrence or death. While some reports have indicated that women operated on during certain times of their menstrual period are at higher risk of recurrence of breast cancer, most studies have not found any difference in results regardless of when breast cancer surgery is performed. Thus, it remains standard procedure to perform breast cancer surgery as soon as a woman has been informed of her options and she is ready to proceed.

SUBPROJECT PROGRESS:

We have enrolled 2 patients into this study and both are in long term follow-up and doing well. This study is closed to accrual therefore there is no recruitment plan and there will be no changes made to the protocol. There are no unexpected safety concerns. There are no publications that cited the GCRC.

SPID: 0286	PROTOCOL: 286	TYPE: RESEARCH
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SHORT TITLE: NSABP B-27

LONG TITLE: NSABP B-27 A Randomized Trial Comparing Preoperative Doxorubicin (Adriamycin Cyclophosphamide) (AC) to Preoperative AC Followed by Preoperative Docetaxel (Taxotere) and to Preoperative AC Followed by Postoperative Docetaxel in Patients with Operable

AIDS:	N	TOTALS	A	B	D
		Inpatient	0	0	0
START DATE:	11/30/1996	Scatter Bed	0	0	0
Total # pts expected for entire study:	10	Outpatient	0	2	0
		Scatter RN Hours	0	0	0
		Offsite Visits	0	1	0

RESEARCH BIONUTRITION	N	MULTICENTER STUDY	Y	
INFORMATICS CORE	Y	CLINICAL TRIAL	Y	Phase III
BIostatistician	N	CORE LAB	N	
ANCILLARIES ONLY	N			

INVESTIGATOR	DEPARTMENT	NON-HOST INSTITUTION: STATE, COUNTRY
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KURTZMAN, SCOTT MD	Surgery	
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SUBPROJECT DESCRIPTION:

The primary aim of this study is to determine whether four cycles of preoperative or postoperative Taxotene given after for cycles of preoperative Adriamycin; (A) and cyclophosphamide (C) (AC) will more effectively prolong disease-free survival (DFS) and survival (S) than do four cycles of preoperative AC alone. The study will also evaluate the effect of the administration of preoperative Taxotene after preoperative AC with respect to clinical and pathologic loco-regional tumor response and conservation. Women with palpable, operable carcinoma of the breast diagnosed by age, clinical tumor size, and clinical nodal status, then randomized to one of three groups. Group I will receive four cycles of preoperative A and C given at 60 mg/m² and 500 mg/m², respectively, every 21 days followed by surgery (lumpectomy and axillary node dissection, or modified radical mastectomy). Group II will receive four cycles of preoperative AC as in group I, followed by four cycles of preoperative Taxotere at 100 mg/m² as a 1-hour infusion every 21 days followed by surgery. Group III will receive four cycles as AC as in groups I and II, followed by surgery and by four cycles of postoperative Taxotere, as in group II. Beginning on the first day of administration of their assigned chemotherapy, all three groups will receive tamoxifen at 20 mg p.o. once daily for 5 years. In all three groups, tumor measurements will be obtained after each cycle of preoperative chemotherapy. Assessment of response will be performed after completion of all preoperative chemotherapy and before surgery. For patients in group II, an additional assessment of response will be performed after completion of AC chemotherapy. Patients in groups I and II who undergo lumpectomy will receive postoperative radiotherapy after their recovery from surgery. Patients in group III who undergo lumpectomy will receive postoperative radiotherapy after their recovery from the fourth cycle of postoperative Taxotere.

SUBPROJECT PROGRESS:

Progress report for the University of Connecticut Health Center is below: Three patients are in long term follow-up and have no evidence of disease and doing well. Four patients have expired due to progression of their disease. Please note that New Britain General Hospital was not under our Institutional Review Board umbrella for this study. There have been no unexpected safety concerns. There have been no publications that have cited the GCRC.

SPID: 0287 **PROTOCOL:** 287 **TYPE:** RESEARCH

SHORT TITLE: NSABP B23

LONG TITLE: NSABP B23 Adriamycin Cyclophosphamide (AC) VS. Cyclophosphamide, methotrexate and 5-fluorouracil (CMF) (pos/neg tamoxifen (TAM) in Node-Negative Breast Cancer

AIDS:	N	TOTALS	A	B	D
		Inpatient	0	0	0
START DATE:	11/1/1996	Scatter Bed	0	0	0
Total # pts expected for entire study:	10	Outpatient	0	0	0
		Scatter RN Hours	0	0	0
		Offsite Visits	0	0	0

RESEARCH BIONUTRITION	N	MULTICENTER STUDY	Y	
INFORMATICS CORE	Y	CLINICAL TRIAL	Y	Phase III
BIostatistician	N	CORE LAB	N	
ANCILLARIES ONLY	N			

INVESTIGATOR	DEPARTMENT	NON-HOST INSTITUTION: STATE, COUNTRY
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KURTZMAN, SCOTT MD Surgery

SUBPROJECT DESCRIPTION:

The specific aims of this protocol are: 1) to determine whether four cycles of AC are superior to six cycles of CMF; and 2) to determine whether Tamoxifen added to Adriamycin Cyclophosphamide or Cyclophosphamide, Methotrexate and 5-fluorouracil is more efficacious than AC or CMF alone.

SUBPROJECT PROGRESS:

This study is now officially closed to follow-up data and we no longer will need to send NSABP information. This study will be terminated within the next month. The three patients we did have on the study did very well, and they are alive and well. There are no safety concerns, no publications citing the GCRC and no interim analysis available at this time.

SPID: 0288	PROTOCOL: 288	TYPE: RESEARCH
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SHORT TITLE:	NSABP B-28
LONG TITLE:	NSABP B-28 Randomized Trial to Evaluate the Worth of Taxol Following Adria/Cyclophosphamide in Breast Cancer Patients with Positive Axillary Nodes

AIDS:	N	TOTALS	A	B	D
		Inpatient	0	0	0
START DATE:	10/1/1996	Scatter Bed	0	0	0
Total # pts expected for entire study:	5	Outpatient	0	3	0
		Scatter RN Hours	0	0	0
		Offsite Visits	0	0	0

RESEARCH BIONUTRITION	N	MULTICENTER STUDY	Y	
INFORMATICS CORE	Y	CLINICAL TRIAL	Y	Phase III
BIostatistician	N	CORE LAB	N	
ANCILLARIES ONLY	N			

INVESTIGATOR	DEPARTMENT	NON-HOST INSTITUTION: STATE, COUNTRY
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KURTZMAN, SCOTT MD	Surgery	
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SUBPROJECT DESCRIPTION:

The primary aim of this study is to determine whether four cycles of Taxol given after four cycles of postoperative Adriamycin (A) and Cyclophosphamide (C) will more effectively prolong disease-free survival and survival than do four cycles of postoperative AC alone in patients with operable breast cancer who have one or more histologically positive axillary lymph nodes.

Patients should have no evidence of metastatic disease and should have undergone either lumpectomy plus axillary node dissection or total mastectomy plus axillary node dissection. Following stratification by number of positive axillary nodes, tamoxifen administration, and type of surgery, patients will be randomly assigned to one of two groups. Group I will receive four cycles of A and C given at 60 mg/m² and 600 mg/m², respectively, every 21 days. Group II will receive four cycles of AC as in Group I, followed by four cycles of Taxol given at 225 mg/m² as a three-hour infusion every 21 days. Beginning on the first day of administration of their assigned chemotherapy, patients \geq 50 years of age and those <50 years of age with tumors that are ER-positive or PgR-positive will receive tamoxifen at 20 mg p.o. once daily for at least five years. All patients in both groups who undergo a lumpectomy, will receive postoperative radiotherapy after completion of their assigned chemotherapy and after any toxicity has resolved.

The objective of this study is to determine whether four cycles of postoperative Taxol given after four postoperative AC will more effectively prolong disease-free survival and survival than will be four cycles of postoperative AC alone in patients with operable breast cancer and histologically positive axillary nodes.

SUBPROJECT PROGRESS:

We have enrolled five patients into the study. Four patients are alive and doing well and one patient expired from her disease. This study is closed to accrual therefore we no longer have a recruitment plan and there are no anticipated changes to the protocol. There have been no unexpected safety concerns with this study. There have been no publications that have cited the GCRC.

SPID: 0290 **PROTOCOL:** 290 **TYPE:** RESEARCH

SHORT TITLE: NSABP P-2: STAR

LONG TITLE: NSABP P-2: Study of Tamoxifen and Raloxifene (STAR) for the prevention of breast cancer.

AIDS:	N	TOTALS	A	B	D
		Inpatient	0	0	0
START DATE:	9/1/1999	Scatter Bed	0	0	0
Total # pts expected for entire study:	60	Outpatient	0	101	0
		Scatter RN Hours	0	0	0
		Offsite Visits	0	1	0

RESEARCH BIONUTRITION	N	MULTICENTER STUDY	Y	
INFORMATICS CORE	Y	CLINICAL TRIAL	Y	Phase III-IV
BIostatistician	N	CORE LAB	N	
ANCILLARIES ONLY	N			

INVESTIGATOR	DEPARTMENT	NON-HOST INSTITUTION: STATE, COUNTRY
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KURTZMAN, SCOTT MD Surgery

SUBPROJECT DESCRIPTION:

In the P-1 study, tamoxifen was shown to prevent the development of invasive and in situ breast cancer. Raloxifene has shown to be an effective drug for the prevention of osteoporosis. It was observed in the Multiple Outcomes of Raloxifene Evaluation (MORE) trial that there were fewer breast cancers in the group of patients that had taken raloxifene compared to the controls. This study will determine if raloxifene is either more or less effective than tamoxifen in reducing the incidence of invasive breast cancer in postmenopausal women who are at increased risk for the disease. A secondary goal is to determine whether raloxifene reduces the endometrial cancer rate compared to tamoxifen.

SUBPROJECT PROGRESS:

No new participants were enrolled this past year. study is closed to enrollment -58 women were randomized to STAR at UCHC -no changes in recruitment plan -no unexpected safety concerns -unblinded -amendment was passed to allow women to change from open label tamoxifen to open label raloxifene; 1 participant chose to crossover

SPID:	0292	PROTOCOL:	292	TYPE:	RESEARCH	
SHORT TITLE:	Cutaneous Immune Response in Lyme Disease and Secondary Syphilis					
LONG TITLE:	Cutaneous Immune Response in Lyme Disease and Secondary Syphilis					
AIDS:	Y	TOTALS		A	B	D
		Inpatient		0	0	0
START DATE:	4/1/1999	Scatter Bed		0	0	0
Total # pts expected for entire study:	100	Outpatient		55	0	0
		Scatter RN Hours		0	0	0
		Offsite Visits		0	0	0
RESEARCH BIONUTRITION	N	MULTICENTER STUDY		N		
INFORMATICS CORE	N	CLINICAL TRIAL		N		
BIostatistician	N	CORE LAB		Y		
ANCILLARIES ONLY	N					

INVESTIGATOR	DEPARTMENT	NON-HOST INSTITUTION: STATE, COUNTRY
RADOLF, JUSTIN D MD	MICROBIAL PATHOGENESIS	
SALAZAR, JUAN C MD	PEDIATRICS	

SUBPROJECT DESCRIPTION:

Venereal syphilis is a chronic inflammatory disorder driven by the persistence of its etiologic agent *Treponema pallidum*. Though the immune/inflammatory response at sites of local treponemal infection may ultimately underlie the development of both protective immunity and clinical manifestations, these local cellular processes have yet to be characterized in humans using the tools of contemporary cellular and molecular immunology. The components of *T. pallidum* that induce these potentially deleterious inflammatory processes also remain poorly characterized. Our understanding of cellular immunity in syphilis is further compromised by our currently limited knowledge concerning the interactions between syphilis and human immunodeficiency virus (HIV) infection. Accordingly, the proposed research has three Specific Aims. In Specific Aim 1, we will perform immunocytochemical analysis of skin biopsies and flow cytometry analysis of leukocytes in suction blisters to characterize cutaneous cellular immune processes in HIV- and HIV+ patients with secondary syphilis. Data from these studies will be correlated with our in vitro research involving immune effector cell activation by *T. pallidum* and treponemal lipoproteins. In Specific Aim 2, we will use the same immunocytochemical and flow cytometric approaches to characterize the cutaneous inflammatory response to synthetic analogs (lipopeptides) of *T. pallidum* lipoproteins. These experiments are an outgrowth of our hypothesis that *T. pallidum* lipoproteins are major inflammatory mediators during syphilitic infection. Building upon our observation that *T. pallidum* lipoprotein analogs induce HIV gene expression in vitro, the experiments in Specific Aim 3 will elucidate the mechanisms which underlie this phenomenon. A principal long-term objective of this research is to elucidate the immune/inflammatory events during syphilitic infection which engender both clinical manifestations and protective immunity. An equally important objective is to obtain cellular and molecular data which will complement our emerging understanding of the interactions between syphilis and HIV infection, including the potential for syphilis to serve as a co-factor for HIV transmission and for HIV infection to alter the clinical course of syphilis.

SUBPROJECT PROGRESS:

Number of subjects enrolled during the reporting period: 72 Number of subjects enrolled since the initiation of the study: 340 Changes in recruitment plans: Institutional Review Board (IRB)-approved form for screening healthy volunteers; no other changes Unexpected safety concerns and their resolution: Subject# /acrostic- 165/ Glbo (enrolled 6/19/06) and subject 171/ Masi (enrolled 8/312/06) had positive Lyme IgM western blot tests, compatible with early Lyme disease. The results were inadvertently overlooked by the coordinator, yet discovered during our February 2007 internal audit. Both subjects were notified of the results and both subjects verbally consented to a retest. Both subjects' Lyme retests were negative for Lyme disease. These results were considered false positives. To prevent future reoccurrences the principal investigator (PI) requested Clinical Lab Medicine automatically sends lab reports for Lyme and rapid plasma reagin (RPR) serology to both the PIs laboratory (Dr. Radolf) and in addition to the co-investigator's (Dr. Salazar) clinical office. This has been accomplished and is working well. Interim data/outcomes (see Moore et al): The primary findings were that (i) phagocytosis of live spirochetes induces markedly greater activation of monocytes and dendritic cells (DCs) in peripheral blood mononuclear cells than do spirochete lysates and (2) human secondary syphilitic sera contains opsonic antibodies that promote internalization of *T. pallidum* by monocytes and DCs. No changes in the protocol are anticipated.

SPID: 0303 **PROTOCOL:** 303 **TYPE:** RESEARCH

SHORT TITLE: The effects of nicotine on bone turnover in older women

LONG TITLE: The effects of nicotine on bone turnover in older women

AIDS:	N	TOTALS	A	B	D
		Inpatient	0	0	0
START DATE:	11/1/1999	Scatter Bed	0	0	0
Total # pts expected for entire study:	160	Outpatient	0	0	0
		Scatter RN Hours	0	0	0
		Offsite Visits	0	0	0

RESEARCH BIONUTRITION	N	MULTICENTER STUDY	N
INFORMATICS CORE	Y	CLINICAL TRIAL	N
BIostatistician	Y	CORE LAB	N
ANCILLARIES ONLY	N		

INVESTIGATOR	DEPARTMENT	NON-HOST INSTITUTION: STATE, COUNTRY
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ONCKEN, CHERYL MD	Medicine	
COONEY, JUDITH PHD	MEDICINE	YALE UNIVERSITY, CT USA
PRESTWOOD, KAREN MD	Medicine	
RAISZ, LAWRENCE G MD	Medicine/Endocrinology	

SUBPROJECT DESCRIPTION:

This study will enroll 150 subjects (smokers, postmenopausal women) to evaluate the effects of smoking cessation with either nicotine replacement or placebo on markers of bone resorption and formation.

SUBPROJECT PROGRESS:

See publications.

SPID: 0322	PROTOCOL: 322	TYPE: RESEARCH
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SHORT TITLE: Circadian Blood Pressure Profile
LONG TITLE: The circadian blood pressure profile, its reproducibility and its relationship to sympathetic nervous system activity, circadian physical activity, sleep quality and novel markers of hypertensive organ damage.

AIDS:	N	TOTALS	A	B	D
			Inpatient	0	0
START DATE: 5/1/2000		Scatter Bed	0	0	0
Total # pts expected for entire study:	150	Outpatient	0	0	0
		Scatter RN Hours	0	0	0
		Offsite Visits	0	0	0

RESEARCH BIONUTRITION	N	MULTICENTER STUDY	N
INFORMATICS CORE	Y	CLINICAL TRIAL	N
BIostatistician	N	CORE LAB	N
ANCILLARIES ONLY	N		

INVESTIGATOR	DEPARTMENT	NON-HOST INSTITUTION: STATE, COUNTRY
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WHITE, WILLIAM MD	Medicine/Hypertension	
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SUBPROJECT DESCRIPTION:

About 20-30% of essential hypertensive patients will have less than the normal (15-20% of awake blood pressure) decline in blood pressure during sleep. This higher than normal sleep blood pressure has been observed during ambulatory blood pressure monitoring and such patients have been termed "non-dippers" to distinguish them from patients with a normal sleep blood pressure decline, "dippers". Patients with nondipping sleep blood pressure are continuously exposed to higher blood pressure levels. This persistent hypertension is likely to be injurious to the endothelium and other organs susceptible to the ill effects of hypertension. Indeed, preliminary studies indicate that nondipper hypertensives have more evidence of hypertensive organ damage. The present study will therefore examine some important issues regarding the criteria for dipper and nondipper categories of blood pressure, the reproducibility of such categorization and the effects of daytime and sleep activity on the decline of blood pressure during sleep. The study will also compare sympathetic nervous system activity, salt sensitivity, and insulin resistance measures in relation to the extent of sleep blood pressure reduction. Finally, endothelial function, retinal vascular structure and left ventricular mass will be compared in dippers and non-dippers.

The project will recruit 150 newly diagnosed and untreated hypertensive subjects to eliminate the effects of drug treatment on blood pressure profiles. After an initial 2-week period when the presence of hypertension will be confirmed by clinic blood pressure readings, patients will undergo 2 separate 24-hour ambulatory blood pressure and electronic activity monitoring sessions about 1-2 weeks apart. During these two periods, awake and sleep sympathetic nervous system activity will be evaluated using plasma and urinary catecholamines. Sleep quality will be measured using a questionnaire and actigraphy derived indices of sleep quality. During the next two weeks and while remaining untreated, all patients will undergo endothelial function studies (B-mode ultrasound), retinal vascular structure assessment (high-resolution retinal photography), and left ventricular mass estimation (echocardiography). In the latter two years of the project, salt sensitivity and its relation to dipper and nondipper blood pressure profiles will be studied.

The reproducibility of the dipper and nondipper categorization will be examined in relation to the effects of sleep and daytime activity, sleep quality, and sympathetic nervous system activity. Direct comparisons between dipper and nondipper groups will be made in salt sensitivity, insulin resistance, and sympathetic nervous system activity. This study will provide information that will be important if clinical trials targeting nocturnal blood pressure are to be designed.

SUBPROJECT PROGRESS:

During 2006, the Principal Investigator (PI), Dr. George Mansoor, left the University and Dr. William White, Division Chief, became the PI of this study. The study did not recruit any new patients for the reporting periods. On June 1 2005, the study was closed to recruitment. There have been no safety concerns during the reporting period. An abstract was presented at the American Society of Hypertension annual meeting in May 2006. The GCRC and National Center for Research Resources were cited on the actual poster. The study is actually closed but there are data awaiting analysis and future publication in 2007 or 2008.

SPID: 0325	PROTOCOL: 325	TYPE: RESEARCH
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SHORT TITLE: Dendritic Type APC-Based Vaccine for Prostate Cancer

LONG TITLE: Dendritic Type Antigen Presenting Cell (APC) -Based Vaccine for Prostate Cancer

	AIDS:	N	TOTALS	A	B	D
			Inpatient	0	0	0
START DATE:		9/7/2000	Scatter Bed	0	0	0
Total # pts expected for entire study:		100	Outpatient	0	0	0
			Scatter RN Hours	0	0	0
			Offsite Visits	0	0	0

RESEARCH BIONUTRITION	N	MULTICENTER STUDY	N
INFORMATICS CORE	Y	CLINICAL TRIAL	N
BIostatistician	N	CORE LAB	N
ANCILLARIES ONLY	N		

INVESTIGATOR	DEPARTMENT	NON-HOST INSTITUTION: STATE, COUNTRY
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CHAKRABORTY, NITYA G PHD	Medicine	
MUKHERJI, BIJAY MD	Medicine	
TAXEL, PAMELA MD	Medicine	

SUBPROJECT DESCRIPTION:

The overall goal of this study is to develop an effective form of active specific immunotherapy for prostate cancer based on the fundamental principles of T lymphocyte activation and molecular mechanism of antigen processing and presentation. The project is based upon the hypothesis that antigen presenting cells (APC) grown from prostate cancer patients will be able to successfully present the prostate specific membrane antigen derived peptides to cytotoxic T lymphocyte (CTL) precursors to induce a specific CTL response in in vitro co-cultures. The idea is to develop an in vitro model system consisting of prostate cancer patients who are human leukocyte antigen (HLA) A2+ and who have very high levels of serum prostate specific antigen (PSA). The question is whether or not it is possible to induce a peptide specific CTL response in vitro, by presenting one of four PSA gene derived epitopes, exhibiting binding motif for HLA A2 molecules, on autologous APC.

SUBPROJECT PROGRESS:

No new subjects were enrolled during the reporting period. We have recently applied to the Institutional Review Board to increase the total number of subjects to be recruited for the study. There were no unexpected safety concerns or changes made to the protocol.

SPID: 0329	PROTOCOL: 329	TYPE: RESEARCH
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SHORT TITLE: ACSOG-Z0010

LONG TITLE: ACSOG-Z0010 A Prognostic Study of Sentinel Node and Bone Marrow Micro-metastases in Women with Clinical T1 or T2 N0M0 Breast Cancer

AIDS:	N	TOTALS	A	B	D
		Inpatient	0	0	0
START DATE:	5/28/2002	Scatter Bed	0	0	0
Total # pts expected for entire study:	20	Outpatient	0	0	0
		Scatter RN Hours	0	0	0
		Offsite Visits	0	0	0

RESEARCH BIONUTRITION	N	MULTICENTER STUDY	Y	
INFORMATICS CORE	Y	CLINICAL TRIAL	Y	Phase III
BIostatistician	N	CORE LAB	N	
ANCILLARIES ONLY	N			

INVESTIGATOR	DEPARTMENT	NON-HOST INSTITUTION: STATE, COUNTRY
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KURTZMAN, SCOTT MD	Surgery	
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SUBPROJECT DESCRIPTION:

Prior to the development of this new procedure, sentinel lymph node dissection (SLND), the only way to identify if the tumor had spread to the nodes in the armpit was to remove all the lymph nodes from the armpit. Numerous studies have shown that removing all of the lymph nodes does not affect survival even though the cancer may come back under the arm. It is possible that removal of the lymph nodes from the middle and lower areas of the armpit (Level I and II) is no better than removing just the sentinel lymph node(s). In 1995, Giuliano et al. conducted a study comparing a SLND with immunohistochemistry (IHC) to routine axillary lymph node dissection (ALND). SLND detected nodal metastases in 42% of all patients, and of these, 45% had micrometastases. The main objectives of this study are: 1) to estimate the prevalence and to evaluate the prognostic significance of sentinel node micrometastases detected by IHC, 2) to estimate the prevalence and to evaluate the prognostic significance of bone marrow micrometastasis detected by immunocytochemistry (ICC) for the first 3600 women, 3) to evaluate the hazard rate for regional recurrence in women whose sentinel nodes are negative by hematoxylin and eosin (H&E) staining, and 4) to provide a mechanism for identifying women whose sentinel nodes contain metastases detected by H&E so that these women can be considered candidates for Study Z001. Women with clinical T1 or T2 NO MO breast cancer will undergo breast-conserving therapy (BCT), bilateral iliac crest bone marrow aspirations, and sentinel lymph node dissection (SLND). When a sentinel node is not identified during the SLND, an ALND is performed. Patients who have no sentinel lymph node metastasis by H&E will not have an ALND. Patients with evidence of metastatic disease in the sentinel node may be eligible for registration and randomization to Study Z0011.

SUBPROJECT PROGRESS:

We have enrolled 9 patients into this study. All 9 patients are now in long term follow-up and are doing well. This study is closed to accrual therefore there is no longer a recruitment plan. There are no unexpected safety concerns and no anticipated changes to the protocol. There have been no publications that have cited the GCRC.

SPID: 0336 **PROTOCOL:** 336 **TYPE:** RESEARCH

SHORT TITLE: Fiber-Reinforced Composites in Dental Implants

LONG TITLE: The use of fiber-reinforced composites in implant dentistry

AIDS:	N	TOTALS	A	B	D
			Inpatient	0	0
START DATE:	6/20/2000	Scatter Bed	0	0	0
Total # pts expected for entire study:	60	Outpatient	87	0	0
		Scatter RN Hours	0	0	0
		Offsite Visits	0	0	0

RESEARCH BIONUTRITION	N	MULTICENTER STUDY	N
INFORMATICS CORE	Y	CLINICAL TRIAL	N
BIostatistician	N	CORE LAB	N
ANCILLARIES ONLY	N		

INVESTIGATOR	DEPARTMENT	NON-HOST INSTITUTION: STATE, COUNTRY
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FREILICH, MARTIN A DDS	Prosthodontics	
GOLDBERG, JON PHD	Biomaterials	
MEIERS, JONATHAN DDS	Prosthodontics	
PENDRYS, DAVID DDS, PHD	Behavioral Sci & Comm Hlth	

SUBPROJECT DESCRIPTION:

Prostheses placed over dental implants are generally made with a metal substructure supporting either a ceramic veneer or resin with artificial plastic teeth. The use of fiber composite technology in the creation of a metal-free implant prosthesis may solve many of the problems associated with this metal alloy substructure such as corrosion, toxicity, complexity of fabrication, high cost and esthetic deficiencies.

Glass fiber-reinforced composites (FRCs) have been developed which have the potential to make an esthetic implant prosthesis substructure utilizing a simple, time-efficient technique. Laboratory and clinical research evaluating FRC prostheses used to restore and replace teeth have shown that these materials exhibit excellent mechanical properties and can form a chemical bond to resin-based veneer materials. Additionally, these FRC materials have the potential to be used to make a single visit, chairside-fabricated provisional tooth replacement bonded to an adjacent anterior tooth prior to implant loading.

SUBPROJECT PROGRESS:

Number of subjects enrolling during the report period-2
 Enrolled since initiation of the study-50
 Any changes in recruitment plans that might be needed-0
 Unexpected safety concerns and their resolution-0
 Interim data and outcomes if appropriate-0
 Any proposed changes made or anticipated in the protocol-0
 Publications, indicating whether the GCRC was cited-0

SPID: 0337 **PROTOCOL:** 337 **TYPE:** RESEARCH

SHORT TITLE: Asthma in Puerto Rican Children

LONG TITLE: The Genetic Epidemiology of Asthma in Puerto Rican Children

AIDS:	N	TOTALS	A	B	D
		Inpatient	0	0	0
START DATE:	6/15/2000	Scatter Bed	0	0	0
Total # pts expected for entire study:	150	Outpatient	2	0	0
		Scatter RN Hours	0	0	0
		Offsite Visits	4	0	0

RESEARCH BIONUTRITION	N	MULTICENTER STUDY	N
INFORMATICS CORE	Y	CLINICAL TRIAL	N
BIostatistician	N	CORE LAB	N
ANCILLARIES ONLY	N		

INVESTIGATOR	DEPARTMENT	NON-HOST INSTITUTION: STATE, COUNTRY
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CLOUTIER, MICHELLE M MD	PEDIATRICS	
LAPIN, CRAIG MD	Pediatrics	
THRALL, ROGER S PHD	MEDICINE/PULMONARY	

SUBPROJECT DESCRIPTION:

Asthma is the most common, chronic disease of children with an incidence that is rising both nationally and worldwide. Asthma is the expression of a combination of genetic predisposition and environmental factors (gene-by-environment interaction) that are the result of a complex interaction between multiple cells, chemical mediators and neural pathways leading to an airway inflammatory response. The goals of this study are to investigate the genetics of asthma in Hispanic/Puerto Rican children and specifically the role of the T lymphocyte receptor (TCR) associated with the gamma/delta chain ("TCR-gamma/delta") and the TCR associated with the alpha/beta chain ("TCR-alpha, beta"). This study utilizes children identified with asthma through an asthma management program called Easy Breathing and a family based trio design (child with asthma, both parents regardless of affectation). We hypothesize that a subset of chromosomal regions associated with T lymphocytes contributes to the asthma phenotype in Hispanic children and that these linkages will vary by asthma severity, bronchial hyper-responsiveness and atopy. We also hypothesize that changes in these regions are associated with functional changes in T cells in the airways. The specific aims of the study are: 1) To examine deoxyribonucleic acid (DNA) from Hispanic children with asthma of varying severity and their parents for 2 gene loci associated with T lymphocytes-specifically, the TCR-delta and the TCR-beta genes using single nucleotide polymorphisms (SNPs). 2) To test these SNP markers in positional candidate genes for linkage/association with asthma phenotype, and specifically, presence of asthma, asthma severity, bronchial hyper-responsiveness, total serum immunoglobulin E (IgE) level, forced expired volume in one second (FEV1) and skin test reactivity to common aeroallergens in family trios identified through Easy Breathing; and 3) To determine whether differences in these regions are associated with changes in T cell function by measuring TCR-gamma, delta and TCR-alpha, beta cells in circulating blood and nasal epithelial cells and the cytokine profiles of nasal cells grown in culture. This study will begin to address the genetic component of this complex gene-by-environment interaction and may help to explain the especially high prevalence of asthma in certain ethnic groups.

SUBPROJECT PROGRESS:

During the time period from 4/01/06 - 12/28/06 we enrolled a total of 21 children into our genetic study (please note that during this time period, this study was labeled as GCRC study #337). During the time period from 12/29/06 - 3/31/07 we enrolled a total of 44 children into our genetic study (please note that during this time period, this study is labeled as GCRC study #626). From 1/26/01 - 5/18/07, we have enrolled a total of 189 children; of this total, 8 children have dropped from the study (we discovered that both parents and grandparents of 3 children were not Puerto Rican, 1 child had a mild case of cerebral palsy and was unable to perform pulmonary function, and 4 children/families were no longer interested in participating). Our primary recruitment strategy consists of distributing a recruitment flyer to 14 area schools, attending parent/teacher conferences, and providing presentations on the topic of asthma at PTO (Parent Teacher Organization) meetings. To date, we have targeted 7 area schools and we plan to continue our recruitment through the summer months at the various Boys and Girls Club locations in Hartford. We will resume school recruitment in Fall 2007 when classes are in session. To date, we have not experienced any unexpected safety issues and we do not anticipate any safety concerns. We have not performed any data analysis; however, we plan to review the interim data when we have completed a total of 200 home visits. Small protocol changes have occurred and each has been reviewed and approved by the Connecticut Children's Medical Center Institutional Review Board (IRB), the IRB of record on 10/06/06: we have begun collecting (1) 4 ml red top

for serum collection. We continue to collect (2) 10 ml purple tops for DNA testing and (1) 4ml purple top for CBC (Complete Blood Count), and (1) 6 ml red top for RAST and IgE testing. The amount of blood we draw remains small, and thus, we do not anticipate any additional risk to our participants. To date, the blood drawing has been very well tolerated by the children. We do not foresee additional changes to the protocol. To date, we have not published any work related to the "Genes, Home Allergens and Asthma in Puerto Rican Children" study.

SPID: 0340	PROTOCOL: 340	TYPE: RESEARCH
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SHORT TITLE: Genetics of Cocaine Dependence

LONG TITLE: Genetics of Cocaine Dependence

AIDS:	N	TOTALS	A	B	D
		Inpatient	0	0	0
START DATE:	6/15/2000	Scatter Bed	0	0	0
Total # pts expected for entire study:	500	Outpatient	95	0	0
		Scatter RN Hours	0	0	0
		Offsite Visits	0	0	0

RESEARCH BIONUTRITION	N	MULTICENTER STUDY	Y
INFORMATICS CORE	N	CLINICAL TRIAL	N
BIostatistician	N	CORE LAB	Y
ANCILLARIES ONLY	N		

INVESTIGATOR	DEPARTMENT	NON-HOST INSTITUTION: STATE, COUNTRY
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KRANZLER, HENRY R MD	PSYCHIATRY	
GELERNTER, JOEL E MD	PSYCHIATRY	YALE UNIVERSITY, CT USA
HERNANDEZ-AVILA, CARLOS MD	Psychiatry	
HESELBROCK, VICTOR M PHD	PSYCHIATRY	
ROUNSAVILLE, BRUCE J MD	PSYCHIATRY	YALE UNIVERSITY, CT USA

SUBPROJECT DESCRIPTION:

Cocaine dependence (CD) has been shown in twin and family studies to have a genetic contribution. This is a multi-center study recruiting affected sibling pairs and other nuclear family members. A genome scan will make it possible to identify regions containing genes that influence risk of CD.

SUBPROJECT PROGRESS:

We have recruited 137 participants for this study between 4/1/06 and 3/31/07. We have recruited 675 total subjects in the study. We continue recruitment of probands only in addition to our previous recruitment of sibling pairs and family trios. A Certificate of Confidentiality issued from 6/1/06 to 3/31/11- we were previously covered under a certificate that was awarded to Yale University for the original study involving sibling pairs. (Certificate No. DA-06-186 is on file with IRB). A waiver/alteration of informed consent for phone screening phase only; phone script was changed to reflect change in payment from \$75 to \$100. Breath alcohol readings are now done to ensure that participants are able to give informed consent. We are now approved to recruit control subjects via Solutions in Surveys (SIS), a professional survey firm. Partial Health Insurance Portability and Accountability Act (HIPAA) waiver of authorization approved specifically for controls screened by SIS, as it differs considerably from the recruitment process for affected individuals. Limited Data Set agreement as well as Data Use Agreement between UCHC and SIS were also submitted and approved.

SPID: 0355 **PROTOCOL:** 355 **TYPE:** RESEARCH

SHORT TITLE: Shark Cartilage

LONG TITLE: MultiCenter, Open-Ended, Double-Blind, Placebo-Controlled, Phase III Study of AE-941 in Addition to Combined Modality Treatment (Chemotherapy/Radiotherapy) for Locally Advanced Unresectable Non-Small-Cell Lung Cancer

AIDS:	N	TOTALS	A	B	D
		Inpatient	0	0	0
START DATE:	9/1/2000	Scatter Bed	0	0	0
Total # pts expected for entire study:	10	Outpatient	0	0	0
		Scatter RN Hours	0	0	0
		Offsite Visits	0	0	0

RESEARCH BIONUTRITION	N	MULTICENTER STUDY	Y	
INFORMATICS CORE	N	CLINICAL TRIAL	Y	Phase III
BIostatistician	Y	CORE LAB	N	
ANCILLARIES ONLY	N			

INVESTIGATOR	DEPARTMENT	NON-HOST INSTITUTION: STATE, COUNTRY
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HEGDE, UPENDRA MD	Medicine	
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SUBPROJECT DESCRIPTION:

AE-941 is a water soluble shark cartilage extract manufactured by AEterna Laboratories Inc. In pre-clinical studies, AE-941 shows antitumor and antimetastatic activity in a dose-dependent manner. Oral administration of AE-941 at maximal dose (500 mg/kg) to mice grafted with the DA3 mouse mammary adenocarcinoma or with the M27 Lewis Lung Carcinoma resulted in a significant decrease in tumor volume and lung nodule number of 61% and 70%, respectively. AE-941 did not alter body weight as compared to control. These findings are comparable to those obtained with cisplatin with the exception that an efficient dose of cisplatin was linked to body weight loss.

Primary objective:

To assess the effect of AE-941 in addition to induction platinum-based chemotherapy followed by concurrent chemo-radiotherapy on overall survival time in stage IIIA and IIIB unresectable non-small-cell lung cancer (NSCLC).

SUBPROJECT PROGRESS:

The study is closed as of January 2007. We have one patient enrolled onto the study who is being followed up at St. Francis Hospital. No safety concerns have been brought to my attention. Interim data and outcomes are not available. No new patients have been enrolled from 04/01/2006 to 03/31/07. No publications.

SPID: 0357 **PROTOCOL:** 357 **TYPE:** RESEARCH

SHORT TITLE: Genetics of Opioid Dependence

LONG TITLE: Genetics of Opioid Dependence

AIDS:	N	TOTALS	A	B	D
		Inpatient	0	0	0
START DATE:	10/19/2000	Scatter Bed	0	0	0
Total # pts expected for entire study:	460	Outpatient	86	0	0
		Scatter RN Hours	0	0	0
		Offsite Visits	0	0	0

RESEARCH BIONUTRITION	N	MULTICENTER STUDY	Y
INFORMATICS CORE	N	CLINICAL TRIAL	N
BIostatistician	N	CORE LAB	Y
ANCILLARIES ONLY	N		

INVESTIGATOR	DEPARTMENT	NON-HOST INSTITUTION: STATE, COUNTRY
KRANZLER, HENRY R MD	PSYCHIATRY	
GELERNTER, JOEL E MD	PSYCHIATRY	YALE UNIVERSITY, CT USA
HESELBROCK, VICTOR M PHD	PSYCHIATRY	
ROUNSAVILLE, BRUCE J MD	PSYCHIATRY	YALE UNIVERSITY, CT USA

SUBPROJECT DESCRIPTION:

Opioid dependence (OD) risk has been shown by both twin and family studies to have a genetic component. This study is being conducted at UConn and Yale, where small nuclear families (SNFs) containing affected sibling pairs are being recruited. A genome scan will make it possible to identify chromosomal regions containing genes that influence risk of OD.

SUBPROJECT PROGRESS:

We recruited 223 participants for this study between 4/1/06 and 3/31/07. To date, we have recruited 583 subjects in the study. Subject payment has changed from \$75 to \$100 for cases and from \$50 to \$75 for control subjects. We continue recruitment of cases in addition to our previous recruitment of sibling pairs and family trios. A waiver to consent for phone screening phase only was approved as well as minor changes to the phone screen. Breath alcohol reading is also now evaluated to ensure that participants are able to give informed consent.

SPID: 0364	PROTOCOL: 364	TYPE: RESEARCH
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SHORT TITLE:	Marijuana Contingency Management
LONG TITLE:	Contingency Management for Marijuana Dependence

AIDS:	N	TOTALS	A	B	D
		Inpatient	0	0	0
START DATE:	9/25/2000	Scatter Bed	0	0	0
Total # pts expected for entire study:	260	Outpatient	48	0	0
		Scatter RN Hours	0	0	0
		Offsite Visits	0	0	0

RESEARCH BIONUTRITION	N	MULTICENTER STUDY	N
INFORMATICS CORE	Y	CLINICAL TRIAL	N
BIostatistician	N	CORE LAB	N
ANCILLARIES ONLY	N		

INVESTIGATOR	DEPARTMENT	NON-HOST INSTITUTION: STATE, COUNTRY
KADDEN, RONALD M PHD	Psychiatry	
LITT, MARK D PHD	BEHAVIORAL SCI & COMM HLTH	
PETRY, NANCY M PHD	PSYCHIATRY	

SUBPROJECT DESCRIPTION:

The overall goal of this research is to improve treatment outcome for marijuana-dependent individuals. The study will attempt to enhance abstinence over the levels obtained in prior research by combining contingency management with Motivational Enhancement Therapy and Cognitive Behavior Therapy (MET/CBT), providing voucher-based reinforcement for abstinence. This combined intervention will be compared to three other interventions: MET/CBT-only, contingency-management-only, and a control group that receives supportive case management only. Recruitment of 260 marijuana-dependent participants will occur over a three-year period. They will be randomly assigned to one of the four interventions. All treatments will be individual, manualized, and provided on an outpatient basis for 9-sessions. Pretreatment assessments will provide baseline data against which to compare treatment outcomes. Follow-up assessments, at three-month intervals for one year following treatment, will evaluate marijuana and other drug/alcohol use, and psychosocial functioning in several domains. It is anticipated that the intervention combining contingency management and MET/CBT will result in the best outcomes, and that the contingency management and MET/CBT interventions by themselves will each be superior to supportive case management.

SUBPROJECT PROGRESS:

A competitive renewal application for this project was funded in September, 2006, and GCRC support for the renewal period was approved in October 2006. After a period for development of the Research and Treatment manuals, for programming the interactive voice response (IVR) system, and for therapist training, recruitment of training cases began in December 2006, followed by the first Main Phase cases in March 2007. Thus far a total of 11 subjects have been randomized to the three treatment conditions. There are no safety concerns, nor outcomes, to report at this early stage of the research. A few relatively minor administrative changes have been approved by the Institutional Review Board; the only change to the protocol was the addition of a Data and Safety Monitoring Plan that meets the granting agency, National Institute of Drug Abuse, specifications.

SPID: 0365	PROTOCOL: 365	TYPE: RESEARCH
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SHORT TITLE: Selenium and Vitamin E Cancer Prevention Trial (SELECT)

LONG TITLE: Selenium and Vitamin E Cancer Prevention Trial (SELECT)

AIDS:	N	TOTALS	A	B	D
		Inpatient	0	0	0
START DATE:	2/16/2001	Scatter Bed	0	0	0
Total # pts expected for entire study:	100	Outpatient	89	0	0
		Scatter RN Hours	0	0	0
		Offsite Visits	1	0	0

RESEARCH BIONUTRITION	N	MULTICENTER STUDY	Y	
INFORMATICS CORE	N	CLINICAL TRIAL	Y	Phase III
BIostatistician	N	CORE LAB	N	
ANCILLARIES ONLY	N			

INVESTIGATOR	DEPARTMENT	NON-HOST INSTITUTION: STATE, COUNTRY
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ALBERTSEN, PETER MD	Surgery	
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SUBPROJECT DESCRIPTION:

SELECT is a Phase III, double blind, placebo-controlled clinical trial designed to assess the effect of selenium and vitamin E (individually and in combination) on the incidence of prostate cancer as determined by routine clinical management. The accrual goal is 32,400 healthy men nationwide who are 55 years old or older (age 50 years or older for African-American men). Study duration will be twelve years with a five-year uniform accrual period. Participants will receive study supplements from the time of their randomization until the end of the trial period, between seven and twelve years depending upon when the participant was randomized.

SUBPROJECT PROGRESS:

Number of subjects enrolled during the report period and since initiation of the study: # in report period 4/1/06 - 3/31/07: No new participants were enrolled in the Selenium and Vitamin E Cancer Prevention Trial (SELECT) in the report period. One participant transferred into UCHC from the M.D.Anderson SELECT site, and 2 participants moved out of the area and transferred out to other SELECT sites. # since initiation of trial: 60 Any changes in recruitment plans that might be needed: N/A, enrollment to the study is closed Unexpected safety concerns and their resolution: In the report period, the Southwest Oncology Group (SWOG) has not notified us of any new safety concerns. Interim data and outcomes if appropriate: N/A - study is in data collection phase Any proposed changes made or anticipated in the protocol: None known Publications: There have been no publications from the actual research. Publications to date have been on design of the study and the methodology employed. The GCRC was not involved in those areas and was not cited.

SPID: 0372 **PROTOCOL:** 372 **TYPE:** RESEARCH

SHORT TITLE: NSABP B-31
LONG TITLE: NSABP B-31: A Randomized Trial Comparing the Safety and Efficacy of Adriamycin and Cyclophosphamide Followed by Taxol (AC ·T) to That of Adriamycin and Cyclophosphamide Followed by Taxol plus Herceptin (AC ·T+H) in Node-Positive Breast Cancer Patie

AIDS:	N	TOTALS	A	B	D
		Inpatient	0	0	0
START DATE:	12/1/2000	Scatter Bed	0	0	0
Total # pts expected for entire study:	25	Outpatient	0	3	0
		Scatter RN Hours	0	0	0
		Offsite Visits	0	2	0

RESEARCH BIONUTRITION	N	MULTICENTER STUDY	Y	
INFORMATICS CORE	Y	CLINICAL TRIAL	Y	Phase II-III
BIostatistician	N	CORE LAB	N	
ANCILLARIES ONLY	N			

INVESTIGATOR	DEPARTMENT	NON-HOST INSTITUTION: STATE, COUNTRY
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KURTZMAN, SCOTT MD	Surgery	
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SUBPROJECT DESCRIPTION:

The primary aims of the study are 1) to compare the cardiotoxicity of four cycles of Adriamycin and Cyclophosphamide (AC) followed by four cycles of Taxol, with that of the same chemotherapy regimen plus Herceptin, in patients with operable, histologically node-positive breast cancer which overexpresses the HER2 protein; and 2) to determine whether, in this patient population, four cycles of AC followed by four cycles of Taxol and weekly Herceptin for one year is more effective in prolonging survival than four cycles of AC followed by four cycles of Taxol.

SUBPROJECT PROGRESS:

Enrolled 5 patients: 3 patients completed therapy according to protocol: 2 of which have relapsed of which 1 pt is still being treated and 1 expired from her metastatic disease. The third patient is alive and disease free. The remaining 2 patients completed therapy up to the point of their cardiotoxicity then study drug was discontinued, 1 patient cardiotoxicity has resolved w/out sequelae and 1 patient continues to be followed for her sarcoidosis and her cardiac status is good and under control with medication. She is being followed by her cardiologist. New Britain General Hospital performance site: Enrolled 4 patients: 3 patients are alive, doing well without evidence of disease. One is patient has developed a new lung primary for which she is being treated and no recurrence of her breast cancer. This study is closed to accrual, therefore there is no longer a recruitment plan. There are no anticipated changes in the protocol. There are no publications that cite the GCRC.

SPID: 0373 **PROTOCOL:** 373 **TYPE:** RESEARCH

SHORT TITLE: NSABP B-30

LONG TITLE: NSABP B-30: A Three-Arm Randomized Trial to Compare Adjuvant Adriamycin and Cyclophosphamide Followed by Taxotere (AC· T); Adriamycin and Taxotere (AT); and Adriamycin, Taxotere, Cyclophosphamide (ATC) in Breast Cancer Patients with Positive Axillar

AIDS:	N	TOTALS	A	B	D
		Inpatient	0	0	0
START DATE:	12/1/2000	Scatter Bed	0	0	0
Total # pts expected for entire study:	10	Outpatient	0	0	0
		Scatter RN Hours	0	0	0
		Offsite Visits	0	0	0

RESEARCH BIONUTRITION	N	MULTICENTER STUDY	Y	
INFORMATICS CORE	Y	CLINICAL TRIAL	Y	Phase III
BIostatistician	N	CORE LAB	N	
ANCILLARIES ONLY	N			

INVESTIGATOR	DEPARTMENT	NON-HOST INSTITUTION: STATE, COUNTRY
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KURTZMAN, SCOTT MD Surgery

SUBPROJECT DESCRIPTION:

The goals of NSABP B-30 are to evaluate, among women with operable node-positive breast cancer (1) the clinical efficacy of Taxotere in conjunction with a standard two-drug chemotherapy regimen (Adriamycin-cyclophosphamide, AC) and (2) the clinical efficacy of Adriamycin and Taxotere without cyclophosphamide.

SUBPROJECT PROGRESS:

No patients enrolled at UCHC. 5 patients enrolled at New Britain General Hospital. This study is closed to accrual. The patients are now in long term follow-up. No safety concerns, publications indicating GCRC citation nor interim data at this time.

SPID: 0374 **PROTOCOL:** 374 **TYPE:** RESEARCH

SHORT TITLE: NSABP CO-7

LONG TITLE: NSABP CO-7: A Clinical Trial Comparing 5-Fluorouracil (5-FU) Plus leucovorin (LV) and Oxaliplatin with 5-Fluorouracil (5-FU) Plus LV in the Treatment of Patients with Stages II and III Carcinoma of the Colon

AIDS:	N	TOTALS	A	B	D
		Inpatient	0	0	0
START DATE:	12/1/2000	Scatter Bed	0	0	0
Total # pts expected for entire study:	20	Outpatient	0	1	0
		Scatter RN Hours	0	0	0
		Offsite Visits	0	1	0

RESEARCH BIONUTRITION	N	MULTICENTER STUDY	Y	
INFORMATICS CORE	Y	CLINICAL TRIAL	Y	Phase III
BIostatistician	N	CORE LAB	N	
ANCILLARIES ONLY	N			

INVESTIGATOR	DEPARTMENT	NON-HOST INSTITUTION: STATE, COUNTRY
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KURTZMAN, SCOTT MD Surgery

SUBPROJECT DESCRIPTION:

The primary aim of this study is to compare the relative efficacy of Fluorouracil (5-FU) + Leucovorin (LV) + Oxaliplatin (FLOX) with that of 5-FU + LV in prolonging disease-free survival among patients who have undergone a potentially curative resection of a stage II or III carcinoma of the colon. The secondary aim of the study is to compare the relative efficacy of FLOX with that of FL in prolonging Survival (S).

SUBPROJECT PROGRESS:

Seven patients have been enrolled in this study. One subject expired from progressive disease, 1 subject is alive with a recurrence and receiving non study treatment and 5 subjects are alive and doing well. This study is closed to accrual and therefore there is no longer a recruitment plan. There are no anticipated changes being made to the protocol. No unexpected adverse events since the last continuation. There are no publications that have cited the GCRC.

SPID: 0381	PROTOCOL: 381	TYPE: RESEARCH
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SHORT TITLE:	Malaria
LONG TITLE:	Study of the Human Malaria Parasite Plasmodium Falciparum

	AIDS:	N	TOTALS			
				A	B	D
			Inpatient	0	0	0
START DATE:		2/1/2001	Scatter Bed	0	0	0
Total # pts expected for entire study:		17	Outpatient	16	0	0
			Scatter RN Hours	0	0	0
			Offsite Visits	0	0	0

RESEARCH BIONUTRITION	N	MULTICENTER STUDY	Y
INFORMATICS CORE	N	CLINICAL TRIAL	N
BIostatistician	N	CORE LAB	N
ANCILLARIES ONLY	N		

INVESTIGATOR	DEPARTMENT	NON-HOST INSTITUTION: STATE, COUNTRY
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BENMAMOUN, CHOUKRI MD	Microbial Pathology	
ELSHEIKHA, HANY PHD	MICROBIOLOGY	
REYNOLDS, JENNIFER MD	Center for Microbial Patho	

SUBPROJECT DESCRIPTION:

Malaria is by far the world's most important tropical parasitic disease. It causes clinical illness in 300 million to 500 million people, 1.5 million to 2.7 million of whom die. Sub-saharian Africa remains the most malarious region in the world with ninety percent of cases and deaths, mostly among children. In this region, about 30% of outpatient consultations and up to 20% hospital admissions are due to malaria. This causes major disturbance in economic and social development. Malaria cases in the United States are linked to international tourism with about one thousand cases diagnosed and treated each year. Since the mid-1950's malaria prophylaxis has relied mostly on chloroquine because of its effectiveness and, notably its low cost. Chloroquine resistance has become widespread in different parts of the world. Mefloquine and quinine have been used extensively in areas of resistance to chloroquine, and proguanil for prophylaxis and treatment, but resistance to these drugs is becoming a substantial problem. The need for more efficacious and less toxic agents, particularly rational drugs that exploit pathways and targets unique to the parasite, is therefore acute.

Plasmodium falciparum is an important intraerythrocytic protozoan pathogen, responsible for the most severe form of human malaria. The parasite undergoes a number of developmental stages in the human host and multiplies asexually in the red blood cell to effect its clinical symptoms and lethal outcome.

Research in my laboratory focuses on how the malaria parasite responds to changing environmental conditions. Maintaining the parasite in culture is an essential step in our research toward understanding the basic biology of this parasite and future development of a vaccine or new antimalarial drugs. The GCRC supports the study by by drawing blood and transporting the sample to the research lab.

SUBPROJECT PROGRESS:

Number of subjects enrolling during the report period: 12 subject (18 blood draws) - Number of subjects enrolling since initiation of the study: 34 subjects (129 blood draws) - Any changes in recruitment plans that might be needed: Increase enrollement to 35 subjects - Unexpected safety concerns and their resolution: NO - Interim data and outcomes if appropriate: N/A - Any proposed changes made or anticipated in the protocol: NO

SPID: 0399	PROTOCOL: 399	TYPE: RESEARCH
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SHORT TITLE: NSABP- B33

LONG TITLE: NSABP B33 Randomized, Placebo-Controlled Double Blind Trial Evaluating the Effect of Exemestane in Clinical Stage T1-2, NO-1, MO Postmenopausal Breast Cancer Patients Completing at Least Five Years of Tamoxifen Therapy

AIDS:	N	TOTALS	A	B	D
		Inpatient	0	0	0
START DATE:	5/28/2002	Scatter Bed	0	0	0
Total # pts expected for entire study:	15	Outpatient	0	0	0
		Scatter RN Hours	0	0	0
		Offsite Visits	0	2	0

RESEARCH BIONUTRITION	N	MULTICENTER STUDY	Y	
INFORMATICS CORE	Y	CLINICAL TRIAL	Y	Phase II-III
BIostatistician	N	CORE LAB	N	
ANCILLARIES ONLY	N			

INVESTIGATOR	DEPARTMENT	NON-HOST INSTITUTION: STATE, COUNTRY
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KURTZMAN, SCOTT MD	Surgery	
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SUBPROJECT DESCRIPTION:

Currently, patients whose primary breast cancer demonstrated estrogen receptors, receive five years of anti-estrogen treatment with tamoxifen. This has been standard care for many years. There is no data supporting more than five years of tamoxifen use, in fact at least one study showed worse results with more than five years of tamoxifen. There is no treatment offered to patients beyond this other than close observation. Exemestane is a new aromatase inhibitor, i.e. a drug that interferes with the metabolism of steroid hormones. The primary aim of this randomized, placebo-controlled, double-blind clinical trial is to determine whether oral administration of exemestane, for 2 years, in postmenopausal patients with estrogen-receptor-positive (ER+) and/or progesterone-receptor-positive (PgR+) breast cancer (CT 1-3 cNO-1 MO) who have completed 5 years of tamoxifen therapy, will prolong disease-free survival and overall survival when compared with placebo. To be eligible, patients must have completed approximately 5 years of adjuvant tamoxifen therapy (either 10 mg po twice a day or 20 mg po daily), be disease free, and have been resected by lumpectomy and axillary node dissection or by modified radical mastectomy. Eligible patients may have received either adjuvant or neoadjuvant chemotherapy at the time of their breast cancer diagnosis. Following stratification by nodal status, patients will be randomized to receive either exemestane 25 mg po daily or placebo, for 2 years. Another aim of this study is to evaluate the effect of tamoxifen withdrawal on bone and to determine if exemestane has any additional effects on the rate of bone loss resulting from tamoxifen withdrawal. Data for fractures, height, and total serum alkaline phosphatase will be collected on the entire study population.

SUBPROJECT PROGRESS:

We have enrolled 5 patients onto this study. 2 patients decided to stop study drug and are now receiving a new hormonal therapy, 2 patients who completed the study treatment according to the protocol and is doing well, and 1 patient who had progressive disease and is off study treatment and receiving another treatment regimen. There are no changes to the recruitment plan. The study is closed to accrual. No unexpected safety concerns and no anticipated changes to the protocol. The GCRC has not been cited in any publications.

SPID: 0400	PROTOCOL: 400	TYPE: RESEARCH
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SHORT TITLE: NSABP-B34

LONG TITLE: NSABP B34 A Clinical Trial Comparing Adjuvant Clodronate Therapy vs. Placebo in Early Stage Breast Cancer Patients Receiving Systemic Chemotherapy and/or Tamoxifen of No Therapy

AIDS:	N	TOTALS	A	B	D
		Inpatient	0	0	0
START DATE:	1/21/2002	Scatter Bed	0	0	0
Total # pts expected for entire study:	10	Outpatient	0	0	0
		Scatter RN Hours	0	0	0
		Offsite Visits	0	2	0

RESEARCH BIONUTRITION	N	MULTICENTER STUDY	Y	
INFORMATICS CORE	Y	CLINICAL TRIAL	Y	Phase III
BIostatistician	N	CORE LAB	N	
ANCILLARIES ONLY	N			

INVESTIGATOR	DEPARTMENT	NON-HOST INSTITUTION: STATE, COUNTRY
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KURTZMAN, SCOTT MD	Surgery	
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SUBPROJECT DESCRIPTION:

This phase III prospective randomized, double-blind, placebo-controlled trial in women with early-stage breast cancer that will evaluate the worth of clodronate, a second-generation bisphosphonate. Bisphosphonates have been shown to block the breakdown of bones, and in one small open label study, had a beneficial effect on bone metastases in patients with breast cancer. This study's primary aim is to determine whether 1600 mg/day of clodronate administered for 3 years, whether alone or in addition to adjuvant chemotherapy and/or hormonal therapy will improve disease-free survival. This study will also evaluate whether adjuvant clodronate results in a reduction in the incidence of skeletal metastasis, skeletal-related morbidity, non-skeletal metastases, and an improvement in relapse-free survival and overall survival. To qualify for this trial, women must have undergone either a total mastectomy or a lumpectomy with either an axillary dissection or sentinel node biopsy. Patients will be stratified according to age, nodal status and estrogen receptor (ER) and or progesterone receptor (PgR) receptor status. Patients must have no evidence of metastatic disease. The administration of adjuvant chemotherapy and/or tamoxifen will be at the discretion of the investigator. The exact regimen, dose and duration will be at the discretion of the investigator and is not part of the study. It is the addition of either clodronate or placebo that is the subject of this study.

SUBPROJECT PROGRESS:

We have 5 patients on this study. Five patients have completed their study medication and are doing very well. This study is closed to accrual therefore there is no recruitment plan. There have been no publications that have cited the GCRC.

SPID: 0410 **PROTOCOL:** 410 **TYPE:** RESEARCH

SHORT TITLE: Testosterone Effects on Bone and Frailty in Men with Osteoporosis

LONG TITLE: Testosterone Effects on Bone and Frailty in Men with Osteoporosis

AIDS:	N	TOTALS	A	B	D
		Inpatient	0	0	0
START DATE:	10/15/2001	Scatter Bed	0	0	0
Total # pts expected for entire study:	150	Outpatient	41	0	0
		Scatter RN Hours	0	0	0
		Offsite Visits	0	0	0

RESEARCH BIONUTRITION	N	MULTICENTER STUDY	N
INFORMATICS CORE	Y	CLINICAL TRIAL	N
BIostatistician	N	CORE LAB	Y
ANCILLARIES ONLY	N		

INVESTIGATOR	DEPARTMENT	NON-HOST INSTITUTION: STATE, COUNTRY
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KENNY, ANNE M MD	CENTER ON AGING	
ALBERTSEN, PETER MD	Surgery	
PRESTWOOD, KAREN MD	Medicine	

SUBPROJECT DESCRIPTION:

Attention to osteoporosis has largely emphasized women's health, and little attention has focused on the diagnosis and prevention of osteoporotic fractures in men. And yet the disease is also an important problem in men. Testosterone levels decline with advancing age, and severe testosterone deficiency is associated with low bone mass and fracture. Several epidemiologic studies suggest that low testosterone is associated with low bone mass in older men, but this finding is not consistent. Men with hip fracture are found to be testosterone deficient more often than control subjects. Among men over age 70 with testosterone levels below the young normal range, we found differences in bioavailable testosterone accounted for 20% of the variance in femoral neck bone mineral density (FN BMD) values. Additional predictors of FN BMD in this population included body mass index and physical activity, two described parameters of frailty.

Based on these data, testosterone supplementation may be important for bone health and frailty in older men. We will test the hypothesis that testosterone supplementation can increase bone mineral density in older men with hip fracture. We will also evaluate the effects of testosterone on physical health and frailty.

SUBPROJECT PROGRESS:

The study is closed to recruitment. We are in the data analysis phase. We require continued support while preparing manuscripts.

SPID: 0413 **PROTOCOL:** 413 **TYPE:** RESEARCH

SHORT TITLE: The Effect of Risedronate on Bone Turnover and Bone Mass in Older Men Receiving
LONG TITLE: The Effect of Risedronate on Bone Turnover and Bone Mass in Older Men Receiving Neoadjuvant Therapy for Prostate Cancer

AIDS:	N	TOTALS	TOTALS		
			A	B	D
		Inpatient	0	0	0
START DATE:	11/15/2001	Scatter Bed	0	0	0
Total # pts expected for entire study:	60	Outpatient	18	0	0
		Scatter RN Hours	0	0	0
		Offsite Visits	0	0	0

RESEARCH BIONUTRITION	N	MULTICENTER STUDY	N	
INFORMATICS CORE	N	CLINICAL TRIAL	Y	Phase III
BIostatistician	N	CORE LAB	Y	
ANCILLARIES ONLY	N			

INVESTIGATOR	DEPARTMENT	NON-HOST INSTITUTION: STATE, COUNTRY
TAXEL, PAMELA MD	Medicine	
ALBERTSEN, PETER MD	Surgery	
RAISZ, LAWRENCE G MD	Medicine/Endocrinology	

SUBPROJECT DESCRIPTION:

This proposal will examine a therapeutic intervention with risedronate in a population of men at high risk for bone loss. Carcinoma of the prostate gland is the most commonly diagnosed cancer in U.S. men, and is the second leading cause of cancer death. Over the last decade, more and more men are being treated with hormonal suppression therapy for locally advanced disease. Recent studies have shown that such hormonal suppression with Luteinizing Hormone Releasing Hormone (LHRH) agonists leads to rapid bone loss and increased risk of osteoporotic fractures (1). The increased incidence of hip fractures and other fragility fractures in older men is a major public health issue. Hip fractures are costly, increase mortality and significantly compromise the independence and quality of life of the survivors. The potential for compounding this problem in men treated with hormonal suppression for locally advanced prostate carcinoma is the rationale for this study.

SUBPROJECT PROGRESS:

There were 13 subjects enrolled in this time period, and there are a total of 45 subjects. No unexpected safety concerns or change of protocol have been made. The abstract below was presented at the American Society for Bone and Mineral Research in September, '06 as a poster. See below. Risedronate Prevents Early Bone Loss and Increased Turnover in Men Receiving LHRH-agonist Therapy for Prostate Cancer P. Taxel¹, R. Dowsett*², P. Albertsen*², P. Fall*², B. Biskup*², L. G. Raisz¹. ¹Medicine, University of CT Health Center, Farmington, CT, USA, ²University of CT Health Center, Farmington, CT, USA. Prostate cancer, the most commonly diagnosed cancer in men, is often treated with Luteinizing Hormone Releasing Hormone (LHRH) agonists. This therapy can lead to rapid bone loss associated with increased bone turnover and ultimately increased fracture risk. To determine whether these effects can be prevented by bisphosphonate therapy, a double-blind, placebo-controlled, randomized trial of risedronate 35 mg/week versus placebo was carried out in older men with locally advanced prostate cancer during the first 6 months of LHRH-agonist therapy. All men received 600 mg/day calcium carbonate and 400 IU/d of vitamin D. Bone mineral density (BMD) was measured by dual energy x-ray absorptiometry (DXA) at the lumbar spine (LS), femoral neck (FN) and total hip (TH) at baseline and at 6 months. Markers of bone resorption (N-telopeptide, NTX, and deoxypyridinoline, DPD) and bone formation (bone specific alkaline phosphatase, BAP, and osteocalcin, OC) were measured at baseline and 6 months. Data on 29 men, 13 on risedronate and 16 on placebo are reported. The mean age of the risedronate and placebo groups was 73 years. At baseline, BMD, sex hormone and vitamin D levels, and bone resorption and formation markers were not different between the groups. The mean (+ standard deviation) T-score of the LS was 0.38 + 1.49; FN -1.03 + .90; TH -0.31 + 1.09. After 6 months, the risedronate group showed no change in femoral neck and total hip BMD while the placebo group decreased by 1.9 and 2.0 % respectively (p=.024 and .002). LS BMD of the risedronate group increased by 2.3% (p=.002 versus baseline) while the placebo group did not change. Urinary NTX and OC decreased by 21 and 5% in the risedronate group, and NTX and OC increased by 21 and 55% in the placebo group (p=.015 and .01, respectively, between groups). These results are similar to those reported with intravenous bisphosphonates. We conclude that LHRH-agonist therapy produces increased bone turnover and rapid bone loss within six months that can be prevented by risedronate treatment. In view of substantial femoral bone loss in these subjects, preventive therapy and close monitoring is indicated in men receiving hormonal suppression therapy.

SPID: 0417	PROTOCOL: 417	TYPE: RESEARCH
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SHORT TITLE:	Transdermal vs Oral Estrogen Therapy on Adolescents with Turner's Syndrome
LONG TITLE:	Effect of transdermal vs oral estrogen therapy on achieving near final adult height and near peak bone mass in growth hormone treated adolescents with Turner Syndrome

AIDS:	N	TOTALS	A	B	D
		Inpatient	0	0	0
START DATE:	12/20/2001	Scatter Bed	0	0	0
Total # pts expected for entire study:	24	Outpatient	1	0	0
		Scatter RN Hours	0	0	0
		Offsite Visits	0	0	0

RESEARCH BIONUTRITION	N	MULTICENTER STUDY	Y
INFORMATICS CORE	N	CLINICAL TRIAL	N
BIostatistician	N	CORE LAB	Y
ANCILLARIES ONLY	N		

INVESTIGATOR	DEPARTMENT	NON-HOST INSTITUTION: STATE, COUNTRY
YIGIT, SEVKET MD	PEDIATRICS	CONNECTICUT CHILDREN'S MEDICAL, CT USA
ALLEN, HOLLY MD	PEDIATRIC ENDOCRINOLOGY	BAYSTATE MEDICAL CENTER, MA USA
DAVENPORT, MARSHA MD	PEDIATRICS	UNIVERSITY OF NORTH CAROLINA, NC USA
RUBIN, KAREN MD	PEDIATRICS	CONNECTICUT CHILDREN'S MEDICAL, CT USA

SUBPROJECT DESCRIPTION:

Estrogen replacement in Turner Syndrome (TS) is accomplished most commonly using estrogen preparations. Based on preliminary data we hypothesize that transdermal vs. oral estradiol will have more favorable effect on near final adult height (FAH) and near peak bone mass (PBM) in growth hormone (GH) treated adolescents with TS. The aim of the study is to evaluate the effect of transdermal vs. oral estrogen on growth and bone mass and their correlation with growth factor levels, markers of bone turnover and sex steroid levels. This 2 year selectively randomized prospective study involves two treatment groups: equivalent doses of oral vs. transdermal estradiol in combination with standard growth hormone therapy. The TS adolescents ages 12-15 years will be selectively randomized to each group by bone age. Estrogen dose will be gradually increased every 6 months over the two years in both groups mimicking normal puberty. With a sample size of 12 in each group and test significance level of 0.05, we will have an 80% power to detect a 25% difference in growth of two groups. There is no preliminary data in terms of bone mass to evaluate sample size estimation for significant difference between two groups. Statistical analysis of outcome measures will be done with repeated measures analysis of variance.

SUBPROJECT PROGRESS:

Total of 3 subjects were enrolled in the study. Currently one subject is in the study. She developed dysfunctional uterine bleeding and required high dose estrogen treatment. She recovered subsequently but she will not be able to continue the study. The study will be terminated this year because of difficulties in recruitment.

SPID: 0426	PROTOCOL: 426	TYPE: RESEARCH
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SHORT TITLE: The SMART Study

LONG TITLE: A Large, Simple Trial Comparing Two Strategies for Management of Anti-Retroviral Therapy (SMART) for Human Immunodeficiency Virus (HIV) Positive Patients

AIDS:	Y	TOTALS	A	B	D
		Inpatient	0	0	0
START DATE:	11/4/2002	Scatter Bed	0	0	0
Total # pts expected for entire study:	10	Outpatient	14	0	0
		Scatter RN Hours	0	0	0
		Offsite Visits	0	0	0

RESEARCH BIONUTRITION	N	MULTICENTER STUDY	Y	
INFORMATICS CORE	N	CLINICAL TRIAL	Y	Phase III
BIostatistician	N	CORE LAB	Y	
ANCILLARIES ONLY	N			

INVESTIGATOR	DEPARTMENT	NON-HOST INSTITUTION: STATE, COUNTRY
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DIECKHAUS, KEVIN MD	Medicine/Infectious Diseases	
FRIEDLAND, GERALD H MD	MEDICINE/EPIDEMIOLGY	YALE UNIVERSITY, CT USA

SUBPROJECT DESCRIPTION:

The purpose of this study is to compare the long-term clinical consequences of two strategies of antiretroviral (AR) management for the Human Immunodeficiency Virus (HIV): (1) the drug conservation (DC) strategy, a strategy aimed at conserving drugs through episodic use of antiretroviral treatment for the minimum time to maintain CD4+cell count $\times 250$ cells/mm³ -versus- (2) the viral suppression (VS) strategy, a strategy aimed at suppressing viral load as much as possible, immediately following randomization and throughout follow-up, irrespective of CD4+cell count.

The primary objective is to compare the DC group with the VS group for the following:

- Survival
- Incidence of major cardiovascular and metabolic complications
- Incidence of serious disease progression events
- Combined endpoint of clinical disease progression, major cardiovascular and metabolic complications, or death
- Grade 4 adverse events
- Self-reported changes in body appearance
- Prevalence at selected time points of multi-drug resistant (MDR) HIV, and rate of developing MDR HIV
- Adherence to antiretroviral treatment, averaged over follow-up
- Disease progression, death, and other outcomes

SUBPROJECT PROGRESS:

Seven subjects were enrolled, none within this reporting period. The study closed to enrollment on January 10th 2006 and the study will be closing on July 11, 2007. Closeout data will be gathered and submitted after July 11th. No further follow-up is planned after that point. Data from the trial has been presented and published.

SPID: 0428	PROTOCOL: 428	TYPE: RESEARCH
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SHORT TITLE:	NSABP B-31.1: Cardiac Function and Patient Characteristic Correlation
LONG TITLE:	NSABP B-31.1: A Study to Determine the Correlation of Cardiac Function with Patient Characteristics and Blood Markers in Women Enrolled in NSABP B-31

AIDS:	N	TOTALS	A	B	D
			Inpatient	0	0
START DATE:	2/1/2002	Scatter Bed	0	0	0
Total # pts expected for entire study:	10	Outpatient	0	0	0
		Scatter RN Hours	0	0	0
		Offsite Visits	0	0	0

RESEARCH BIONUTRITION	N	MULTICENTER STUDY	Y	
INFORMATICS CORE	N	CLINICAL TRIAL	Y	Phase III
BIostatistician	Y	CORE LAB	N	
ANCILLARIES ONLY	N			

INVESTIGATOR	DEPARTMENT	NON-HOST INSTITUTION: STATE, COUNTRY
KURTZMAN, SCOTT MD	Surgery	

SUBPROJECT DESCRIPTION:

This is a companion study to NSABP B31. This study, NSABP B-31.1, is designed to determine the usefulness of echo cardiography (ECHO) in addition to multi gated acquisition (MUGA) scan in the monitoring of patients' cardiac function. This study offers an excellent opportunity to assess more subtle effects of Herceptin on cardiac function and serum markers. More sensitive and precise measures of Herceptin's cardiac effects may provide important information for early detection and risk stratification of a patient's cardiac characteristics, which in turn may allow the application of preventive measures.

The primary aim of this companion study is to evaluate Herceptin-associated abnormalities via echo cardiographic ally obtained parameters that indicate diastolic dysfunction and correlate these abnormalities with baseline patient characteristics to determine whether such correlations predict which patients are at greatest risk of developing cardiac dysfunction when treated with Adriamycin and cyclophosphamide (AC), followed by Taxol plus Herceptin as part of NSABP B-31.

The secondary aim of this companion study is to determine whether abnormal levels of brain natriuretic peptide (BNP), troponin-T (TnT), troponin-I (TnI), tumor necrosis factor-alpha (TNF- cx), interleukin-1 beta (IL-1fJ), or interleukin-6 (IL-6) correlate with echocardiographic abnormalities that reflect myocardial damage in patients receiving AC followed by Taxol with Herceptin and whether any of these blood markers can serve as early predictors of cardiac dysfunction in this adjuvant setting.

The tertiary aim of this companion study is to evaluate the concordance of left ventricular ejection fraction (L VEF) results measured by MUGA and by ECHO.

The changes in echocardiographic parameters and blood markers will be compared longitudinally in B-31 group 2 patients who will receive Herceptin as well as compared laterally with group 1 patients who will not receive Herceptin. Because this research is exploratory in nature, none of the results obtained from a patient's ECHOs or blood markers will be made known to the patient or her investigator. The data analysis will be descriptive and numerous possible relationships will be considered. A total of 220 B-31 patients will be enrolled. Patients enrolled in B-31.1 are subject to all eligibility criteria defined in NSABP B-31.

SUBPROJECT PROGRESS:

1 patient enrolled, who is in long term follow-up and doing well. This study is closed to accrual therefore there is no recruitment plan at this time. There are no anticipated changes to the protocol and no unexpected safety concerns. There are no publications that have cited the GCRC.

SPID: 0433 **PROTOCOL:** 433 **TYPE:** RESEARCH

SHORT TITLE: Acute Estrogen in Women

LONG TITLE: Acute Effects of Oral Estrogen on Biochemical Markers of Bone Turnover

AIDS:	N	TOTALS	A	B	D
		Inpatient	0	0	0
START DATE:	3/8/2002	Scatter Bed	0	0	0
Total # pts expected for entire study:	6	Outpatient	12	0	0
		Scatter RN Hours	0	0	0
		Offsite Visits	0	0	0

RESEARCH BIONUTRITION	N	MULTICENTER STUDY	N	
INFORMATICS CORE	N	CLINICAL TRIAL	Y	Phase II
BIostatistician	Y	CORE LAB	Y	
ANCILLARIES ONLY	N			

INVESTIGATOR	DEPARTMENT	NON-HOST INSTITUTION: STATE, COUNTRY
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TAXEL, PAMELA MD	Medicine	
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PINTO, PAMELA MD	Medicine	
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SUBPROJECT DESCRIPTION:

This pilot study is an unblinded trial designed to determine whether there is an acute effect of transdermal estrogen on bone resorption in postmenopausal women. Specifically, we will determine the change in markers of bone resorption (C-telopeptide, N-telopeptide, and free deoxypyridinoline) during two weeks of treatment with a transdermal estradiol patch applied biweekly in postmenopausal women over the age of 65 years with estradiol levels less than 10 pg/ml. If a significant early reduction in resorption markers occurs in these women we will plan a larger placebo-controlled trial with additional time points to confirm and extend these pilot data.

SUBPROJECT PROGRESS:

This study is now closed to enrollment. We had 1 additional subject in the current reporting period for a total of 17 women and 11 men (No more men were recruited). We are in the process of analyzing the study data for manuscript preparation.

SPID: 0439 **PROTOCOL:** 439 **TYPE:** RESEARCH

SHORT TITLE: Dendritic Cells (DC) Crosstalk

LONG TITLE: DC-Th Crosstalk in Cytotoxic T Lymphocytes (CTL) Responses to Mart-1

	AIDS:	N	TOTALS			
				A	B	D
			Inpatient	0	0	0
START DATE:		4/25/2002	Scatter Bed	0	0	0
Total # pts expected for entire study:		12	Outpatient	11	0	0
			Scatter RN Hours	0	0	0
			Offsite Visits	0	0	0

RESEARCH BIONUTRITION	N	MULTICENTER STUDY	N
INFORMATICS CORE	Y	CLINICAL TRIAL	N
BIostatistician	N	CORE LAB	N
ANCILLARIES ONLY	N		

INVESTIGATOR	DEPARTMENT	NON-HOST INSTITUTION: STATE, COUNTRY
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MUKHERJI, BIJAY MD	Medicine	
CHAKRABORTY, NITYA G PHD	Medicine	
HEGDE, UPENDRA MD	Medicine	

SUBPROJECT DESCRIPTION:

The major goal of this proposal is to test the hypothesis that Crosstalk in Cytotoxic T Lymphocytes (CTL) response against human thioacetamide acid (TAA) induced by Dendritic Cells (DC)-based stimulation is subject to regulation by DC-Th cross-talks. A better understanding of the rules of the engagement of DC-Th cross-talks that govern the generation and the control of anti-TAA CTL response will have a major impact in DC-based vaccine design.

SUBPROJECT PROGRESS:

Three new subjects were enrolled during the reporting period. No changes were made to the recruitment plans. There were no unexpected safety concerns or changes made to the protocol. There was one new manuscript published.

SPID: 0442	PROTOCOL: 442	TYPE: RESEARCH
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SHORT TITLE:	HALT-C Trial
LONG TITLE:	The Hepatitis C Antiviral Long-Term Treatment Against Cirrhosis (HALT-C)

AIDS:	N	TOTALS	A	B	D
			Inpatient	0	0
START DATE:	5/7/2002	Scatter Bed	0	0	0
Total # pts expected for entire study:	45	Outpatient	52	0	0
		Scatter RN Hours	0	0	0
		Offsite Visits	0	0	0

RESEARCH BIONUTRITION	N	MULTICENTER STUDY	Y	
INFORMATICS CORE	Y	CLINICAL TRIAL	Y	Phase III-IV
BIostatistician	N	CORE LAB	Y	
ANCILLARIES ONLY	N			

INVESTIGATOR	DEPARTMENT	NON-HOST INSTITUTION: STATE, COUNTRY
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BONKOVSKY, HERBERT L MD	MEDICINE/GASTROENTEROL OGY	
AZIZ, KHALID MD	Medicine	

SUBPROJECT DESCRIPTION:

The purpose of this study is to conduct a randomized, controlled trial to determine if long-term interferon therapy can reasonably reduce the risk of histologic progression to cirrhosis, decompensated liver disease and/or hepatocellular carcinoma in patients with chronic hepatitis C and advanced fibrosis or cirrhosis who failed to respond to previous interferon therapy.

Specific aims: 1) To determine if 4 years of interferon therapy will prevent progression of advanced fibrosis to cirrhosis in patients with chronic hepatitis C who failed previous interferon treatment; 2) to determine if 4 years of interferon therapy, in patients with cirrhosis secondary to chronic hepatitis C who failed previous interferon treatment, will a) reduce the risk of developing hepatic decompensation; b) reduce the need for hepatic transplantation; c) reduce the risk of developing hepatocellular carcinoma; and 3) To determine if 4 years of interferon therapy will improve the quality of life in patients with advanced fibrosis or cirrhosis secondary to chronic hepatitis C who failed previous interferon treatment.

Approximately 1200 patients (at all centers) who meet the inclusion/exclusion criteria will be entered into a Lead-in Phase. They will be treated with a combination of Peginterferon alfa-2a and ribavirin for a period of 24 weeks. Patients who have no detectable Hepatitis C Virus (HCV) Ribonucleic Acid (RNA) at week 20 will continue on combination therapy until week 48. Patients who do not clear virus will be randomized 50:50 at week 24 to receive either Peginterferon alfa-2a alone or no further therapy for the next three and a half years. Both randomized groups will be monitored quarterly during these 42 months and biopsies will be obtained at 24 and 48 months after the start of the Lead-in Phase. An estimated 800 patients will be evaluable at the conclusion of the trial.

SUBPROJECT PROGRESS:

Enrollment closed in 2003. We enrolled 37 patients. The target for enrollment was exceeded and nationally there were 1382 patients enrolled in the study. The Halt-C Trial was extended until October 2009 to add an observational period of time in which to gather further data on the natural history of hepatitis C. All patients finished study drug as of January 2007 and are now in the Halt-C extension/observational part of the trial. The Data Safety Monitoring Board last met on 12-Jan-07 and voted unanimously to continue the Halt-C Trial. There were no safety concerns identified. Now that patients have completed the main trial, we are expecting data analysis to study reveal results this year. There have been a number of publications, all of which have cited the University of CT Health Centers GCRC. See publications.

SPID:	0445	PROTOCOL:	445	TYPE:	RESEARCH	
SHORT TITLE:	Feasibility of SH2 Domain Profiling					
LONG TITLE:	Feasibility of Src Homology 2 (SH2) Domain Profiling as a Molecular Diagnostic Tool for Patients					
AIDS:	N	TOTALS		A	B	D
		Inpatient		0	0	0
START DATE:	6/20/2002	Scatter Bed		0	0	0
Total # pts expected for entire study:	60	Outpatient		0	0	0
		Scatter RN Hours		0	0	0
		Offsite Visits		0	0	0

RESEARCH BIONUTRITION	N	MULTICENTER STUDY	N
INFORMATICS CORE	Y	CLINICAL TRIAL	N
BIostatistician	N	CORE LAB	N
ANCILLARIES ONLY	N		

INVESTIGATOR	DEPARTMENT	NON-HOST INSTITUTION: STATE, COUNTRY
MAYER, BRUCE J PHD	GENETICS & DEV BIOLOGY	
DECKERS, PETER MD	Surgery	
KURTZMAN, SCOTT MD	Surgery	
ZARFOS, KRISTEN MD	Surgery	

SUBPROJECT DESCRIPTION:

There is a need for molecular diagnostic tools that will allow the classification of tumors beyond what is currently possible using standard techniques. Ideally markers will be identified that will have prognostic value (correlate with response to particular treatments, for example). Expression profiling using cDNA microarrays is now being tested for this purpose, but is at present cumbersome, costly, and is unlikely to give any information about the molecular defects in the tumor cell. We are developing a novel molecular diagnostic technique based on the profile of proteins in a tumor sample that bind to certain protein domains known to play an important role in signal transduction. In preliminary experiments this technique can identify different binding profiles in hematological malignancies, suggesting it may be a valuable molecular diagnostic tool. The resulting profiles may also be informative about the molecular defects in a particular tumor. To date we have not tested the method on solid tumor samples. We propose to test this technique on samples of breast cancers available at the UCHC to establish the feasibility of implementation on a larger scale. Ultimately, if the technique is sufficiently robust and reproducible, we will correlate profiling data with patient information to determine whether the interaction profiling provides information with prognostic value.

SUBPROJECT PROGRESS:

No new patients were enrolled in this study in the past year. Poor recruitment has been an ongoing problem. To address this we have been collaborating with Dr. Kevin Claffey to take advantage of breast cancer samples that he has obtained for his own studies, and we have also embarked on a collaboration with investigators at other institutions with access to samples associated with clinical outcomes data. While we will still make some attempts to obtain new samples from UCHC, our major efforts from this point on will be to use samples obtained through collaborations. We would still like to use GCRC staff to coordinate the study, as this has been extremely valuable in maintaining databases with patient coding information, and in coordinating Institutional Review Board approvals. We have a manuscript describing the use of our SH2 profiling method in press, and anticipate that a publication describing SH2 profiling of breast cancer samples obtained through this study and through collaborations will be submitted within the next year.

SPID: 0446	PROTOCOL: 446	TYPE: RESEARCH
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SHORT TITLE: Network and Contingency Management for Alcohol Treatment

LONG TITLE: Network and Contingency Management for Alcohol Treatment

AIDS:	N	TOTALS	A	B	D
		Inpatient	0	0	0
START DATE:	6/20/2002	Scatter Bed	0	0	0
Total # pts expected for entire study:	140	Outpatient	0	0	0
		Scatter RN Hours	0	0	0
		Offsite Visits	0	0	0

RESEARCH BIONUTRITION	N	MULTICENTER STUDY	N
INFORMATICS CORE	N	CLINICAL TRIAL	N
BIostatistician	Y	CORE LAB	N
ANCILLARIES ONLY	N		

INVESTIGATOR	DEPARTMENT	NON-HOST INSTITUTION: STATE, COUNTRY
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LITT, MARK D PHD	BEHAVIORAL SCI & COMM HLTH	
KADDEN, RONALD M PHD	Psychiatry	
PETRY, NANCY M PHD	PSYCHIATRY	

SUBPROJECT DESCRIPTION:

Relapse is the most serious problem in alcoholism treatment. The overall aim of the present study is to determine if a treatment directed at changing the patient's social network, from one that reinforces drinking behavior to one that reinforces sobriety, can create the conditions necessary for long-term treatment success. In addition, we intend to determine if explicit reinforcement for this change of social network (Contingency Management or ContM) will be more effective than the same network support intervention without contingent reinforcement for change.

207 alcohol dependent men and women will be recruited and assigned to one of three treatments in a dismantling design intended to evaluate the relative contributions of Network Support and Contingency Management over a Case Management control condition. The three conditions will be: Case Management, Network Support, and Network Support + ContM. The Network support intervention is based on the 12-Step Facilitation intervention used in Project MATCH, but will focus more on Alcoholics Anonymous as an alternative social network, with additional network-building activities built in. Network Support + ContM (Condition 3) should yield the best results. Reinforcement will be provided contingent upon completing steps of treatment (e.g., Steps 1-6 of 12-step treatment, attending AA meetings, non-drinking social activities) is expected to result in high adherence to treatment and therefore a more complete change of social network. Change in social network should lead to more enduring abstinence. More favorable long-term outcomes should result as a function of network support for sobriety, measured at follow-up points up to 2 years post-treatment. We will also explore the possibility, introduced in Project MATCH, that a change in network support will be maximally beneficial to those whose social networks were initially most supportive of drinking to start with.

SUBPROJECT PROGRESS:

212 subjects enrolled since initiation of trial. No changes in recruitment plans needed. No safety concerns. Findings to date: Alcohol dependent men and women (N=210) recruited from the community were randomly assigned to one of three outpatient treatment conditions: Network Support (NS), Network Support + Contingency Management (NS+CM), or Case Management (CaseM, a control condition). Analysis of drinking rates for 193 participants at Posttreatment indicated a significant main effect for Treatment Type, with both Network Support conditions yielding better outcomes than the CaseM condition. Analyses of social network variables at posttreatment indicated that the NS conditions did not reduce social support for drinking, but did increase social support for abstinence, as well as AA involvement. Both the network support variables and the AA involvement variables were significantly correlated with drinking outcomes. These findings indicate that drinkers social networks can be changed by a treatment that is specifically designed to do so, and that these changes contribute to improved drinking outcomes. No changes made or anticipated in protocol.

SPID: 0448 **PROTOCOL:** 448 **TYPE:** RESEARCH

SHORT TITLE: Soy and Isoflavones
LONG TITLE: The Effect of Soy Protein and Isoflavones on Bone on Older Women

AIDS:	N	TOTALS	A	B	D
		Inpatient	0	0	0
START DATE:	7/16/2002	Scatter Bed	0	0	0
Total # pts expected for entire study:	160	Outpatient	0	0	0
		Scatter RN Hours	0	0	0
		Offsite Visits	0	0	0

RESEARCH BIONUTRITION	N	MULTICENTER STUDY	N
INFORMATICS CORE	N	CLINICAL TRIAL	N
BIostatistician	Y	CORE LAB	N
ANCILLARIES ONLY	N		

INVESTIGATOR	DEPARTMENT	NON-HOST INSTITUTION: STATE, COUNTRY
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KENNY, ANNE M MD	CENTER ON AGING	
KERSTETTER, JANE PHD	NUTRITIONAL SCIENCE	UConn - Storrs, CT USA

SUBPROJECT DESCRIPTION:

Osteoporosis is a disease that primarily affects older women in the United States. Epidemiological studies report decreased hip fracture incidence in Asian countries where the population ingests larger amounts of soy than is contained in the average US diet. Recent data suggest that soy intake is correlated with bone mineral density in Asian women. Soy foods are rich sources of isoflavones and these compounds may be responsible for the health benefits of soy. Although epidemiological and preliminary cross-sectional data suggest that soy may be beneficial to bone (1,2), few well-controlled clinical trials have been completed to adequately test this theory. Many women in the United States are demanding more 'natural' treatments for chronic diseases and a substantial proportion of women are already consuming more soy products or using isoflavone supplements. However, it is unclear if these practices are beneficial to postmenopausal women. We hypothesize that isoflavones and soy protein will have a beneficial effect on bone in older women compared to control protein. Further, we hypothesize that there will be an additional benefit to bone in women who receive soy protein plus isoflavones compared to control protein or soy protein alone. In order to test these hypotheses we propose an 1-year nutrition intervention study in women over age 65 years in which the main outcome measures will be biochemical markers of bone turnover, quality of life, bone mineral density.

SUBPROJECT PROGRESS:

The study was completed in August 2005. 99 women completed. Presently we are analyzing data and preparing manuscripts. There were no safety concerns. There is no interim data. We will still need GCRC support for ongoing laboratory analysis and statistical assistance.

SPID: 0451	PROTOCOL: 451	TYPE: RESEARCH
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SHORT TITLE: Leukapheresis in Selected Patients

LONG TITLE: Leukapheresis in Selected Patients

AIDS:	N	TOTALS	A	B	D
			Inpatient	0	0
START DATE:	6/30/2002	Scatter Bed	0	0	0
Total # pts expected for entire study:	10	Outpatient	0	0	0
		Scatter RN Hours	0	0	0
		Offsite Visits	0	0	0

RESEARCH BIONUTRITION	N	MULTICENTER STUDY	N
INFORMATICS CORE	Y	CLINICAL TRIAL	N
BIostatistician	N	CORE LAB	N
ANCILLARIES ONLY	N		

INVESTIGATOR	DEPARTMENT	NON-HOST INSTITUTION: STATE, COUNTRY
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MUKHERJI, BIJAY MD	Medicine	
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SUBPROJECT DESCRIPTION:

It has been well-established that tumors can elicit an immune response and that strategies which target the immune response can result in tumor regression. However, the precise mechanisms for tumor recognition and destruction remain inadequately defined, and correlation of anti-tumor immunity in the lab with clinical reductions in tumor size has been difficult.

Because of the longstanding interest at University of Connecticut Health Center in tumor immunology, many patients have been treated on clinical trials with some type of immunotherapy or tumor vaccine. Detailed analysis of the ability of these patients to respond to tumors may contribute to better understanding of the immune response to cancer and to the development of more effective therapies.

This protocol proposes to perform outpatient leukapheresis to increase the number of patient lymphocytes available for study. This will be performed on patients who have previously been treated on a tumor vaccine protocol at UCHC, and also on a small number of normal controls.

SUBPROJECT PROGRESS:

Four subjects were enrolled since the study inception in 2002. During this reporting period, there were no changes made to the recruitment plan. There were no unexpected safety concerns or changes made to the protocol. Due to the limited activity, this study was closed in the GCRC on November 30, 2006. IRB # 00-030 Chattopadhyay S, Mehrotra S, Chhabra A, Chakraborty NG, and Mukherji B. Effects of CD4+CD25+ and CD4+CD25- regulatory T cells on the activation and expansion of self epitope and non-self epitope specific CTL precursors, in vitro. *J. Immunol.* 176:984-990, 2006. IRB # 00-030 Chhabra A, Mehrotra S, Chakraborty NG, Dorsky DI, Mukherji B. Activation Induced Cell Death of Human Melanoma Epitope Specific Primary Cytotoxic T Lymphocytes mediated by the release of Mitochondrial Apoptosis Inducing Factor. *Eur. J. Immunol.* 3: 3167-3174, 2006. IRB # 06-137 Mehrotra S, Chhabra A, Chakraborty NG, Mukherji B. Inhibition of c-Jun-Terminal Kinase (JNK) Rescues influenza epitope specific human cytolytic T lymphocytes (CTL) from activation induced cell death (AICD). *J. Leuc. Biol.* 81 539-547, 2007.

SPID: 0453 **PROTOCOL:** 453 **TYPE:** RESEARCH

SHORT TITLE: Diabetes, Depression, & Coronary Heart Disease
LONG TITLE: Pilot Study of the Relationship Between Diabetes, History of Depression, and Coronary Heart Disease (CHD) in Post-Menopausal Women

	AIDS:	N	TOTALS			
				A	B	D
			Inpatient	0	0	0
START DATE:		7/12/2002	Scatter Bed	0	0	0
Total # pts expected for entire study:		80	Outpatient	28	0	0
			Scatter RN Hours	0	0	0
			Offsite Visits	0	0	0

RESEARCH BIONUTRITION	N	MULTICENTER STUDY	N
INFORMATICS CORE	Y	CLINICAL TRIAL	N
BIostatistician	Y	CORE LAB	Y
ANCILLARIES ONLY	N		

INVESTIGATOR	DEPARTMENT	NON-HOST INSTITUTION: STATE, COUNTRY
WAGNER, JULIE PHD	Behavioral Sci & Comm Hlth	
SEIP, RICHARD PHD	PREVENTIVE CARDIOLOGY	HARTFORD HOSPITAL, CT USA
THOMPSON, PAUL MD	PREVENTIVE CARDIOLOGY	HARTFORD HOSPITAL, CT USA

SUBPROJECT DESCRIPTION:

Diabetes and depression both independently put women at increased risk for coronary heart disease (CHD). Thus, a better understanding of how these risk factors interact is crucial to our understanding of heart disease in women. One hypothesized mechanism for the depression-diabetes-CHD relationship is the Hypothalamic-Pituitary-Adrenal (HPA) axis and cortisol production. Currently, no data have been published that look at these variables in concert. Thus, it is unclear if they each convey an individual risk that becomes additive when combined, or if they interact to convey multiplicative risk.

The study being proposed is a cross sectional study of depression, diabetes, and CHD risk in women. The research design is a 2X2 factorial design. The sample will consist of 80 age-matched postmenopausal women. The independent variables are 1) presence of a history of depression (yes or no), and 2) T2DM status (yes or no). The dependent variables are salivary cortisol levels, lipids (total cholesterol, HDL subfractions, and triglycerides), waist-to-hip ratio, brachial artery flow mediated dilation, hemostatic indicator (vWF), inflammatory marker (c-reactive protein), microalbuminuria, and blood pressure. Variables that will be controlled for include BMI (Bone Mass Index), lipid lowering agents, beta blockers, ACE inhibitors, antihypertensive agents, and history of smoking, physical activity, and alcohol use.

Three hypotheses will be tested: 1) There will be a main effect for diabetes, such that participants with diabetes will show higher WHR, blood pressure, vWf, C-Reactive Protein (CRP), dyslipidemia, microalbuminuria, and more impaired endothelium dependent brachial reactivity (EDBR) than those without diabetes; 2) There will be a main effect for history of depression, such that participants a positive history will show higher WHR, blood pressure, vWf, CRP, microalbuminuria, more impaired EDBR, and a flatter cortisol pulsatile circadian rhythm than those with a negative history; 3) there will be an interaction between history of depression and diabetes, such that participants with both diabetes and positive history of depression will show higher WHR, blood pressure, vWf, CRP, and more impaired EDBR, than those with only history of depression or diabetes.

SUBPROJECT PROGRESS:

From 4/1/2006 until 3/31/2007, 17 women enrolled. Two were found to be ineligible during the first visit and excluded from participation, for a total of 15 eligible participants during this period. To date, 132 subjects have been enrolled and 105 have been eligible and able to fully participate (24 women were excluded from the study after Informed Consent Form (ICF) was obtained and during first visit data collection. This was because it was discovered during first visit that they did not meet set criteria to complete the study. Three withdrew from the study due to health reasons unrelated to the study). Modifications to the project approved by Institutional Review Board (IRB) this year include: 1) Approval for Dr. Neil Gray (of Hartford Hospital) to contact his patients to invite them to participate in the study, 2) A partial waiver of consent solely for the phone screen phase of the study 3) Addition of 8 standardized self-report assessments to survey packet 4) Approval of a script to be used for radio advertising 5) Approval of a change in staff removing Dr. George Mansoor (who is no longer with UCHC) and Dr. Richard Siep (who is no longer with Hartford Hospital) from the study team. Drs. William White and Madhavi Mallareddy were added as co-investigators 6) Changes were made to

ICF and protocol to reflect the above changes. There are no unexpected safety concerns.

Preliminary results. [Abstract] International Journal of Behavioral Medicine, p. 285. Wagner, J., Tennen, H., Mansoor, G., Abbott, G. (2006). History of remitted major depressive disorder and glycemic control in postmenopausal diabetic women. [Abstract] International Journal of Behavioral Medicine, p. 236.

Abbott, G., Wagner, J. (2006). Marital relationship, depression, and diabetes in postmenopausal women. [Abstract] International Journal of Behavioral Medicine, p. 265.

Wagner J, Tennen, H (2005). Diabetes, metformin, and history of depression: Associations with urinary albumin in women. [Abstract]. Psychosomatic Medicine, 67(1), A73.

Wagner, J., Mansoor, G. (2006). Brachial artery reactivity in post-menopausal women with type 2 diabetes: Predictors of vasodilation vs constriction. [Abstract] Diabetes;707p.

Wagner, J., Tennen, H., Abbott, G. (2006). Relationships among history of remitted depression and temporally distal physical and emotional symptoms and functioning in postmenopausal women with Type 2 diabetes. [Abstract] Diabetes;1872-p.

Wagner J, Tennen, H (2005). Diabetes, metformin, and history of depression: associations with urinary albumin in women. [Abstract] Psychosomatic Medicine, 67(1), A73.

Wagner, J. Diabetes, Metformin, & History of Depression: Associations with Urinary Albumin in Women. [Abstract] Proceedings of the Womens Health Interdisciplinary Research Symposium, P30. National Institutes of Health, Bethesda, MD, 2004.

MANUSCRIPTS UNDER REVIEW Wagner J, Tennen H, Mansoor G, Abbott G. Endothelial dysfunction and history of depression in post-menopausal women with type 2 diabetes: A case control study. Wagner J, Tennen H. History of major depressive disorder and diabetes outcomes among postmenopausal women. Journal of General Internal Medicine.

SPID: 0455 **PROTOCOL:** 455 **TYPE:** RESEARCH

SHORT TITLE: SH2 Binding as Prognostic Indicator

LONG TITLE: Feasibility of Src Homology 2 (SH2) Binding as a Prognostic Indicator: A retrospective study of archived breast cancer samples

AIDS:	N	TOTALS	A	B	D
		Inpatient	0	0	0
START DATE:	9/20/2002	Scatter Bed	0	0	0
Total # pts expected for entire study:	300	Outpatient	0	0	0
		Scatter RN Hours	0	0	0
		Offsite Visits	0	0	0

RESEARCH BIONUTRITION	N	MULTICENTER STUDY	N
INFORMATICS CORE	Y	CLINICAL TRIAL	N
BIostatistician	N	CORE LAB	N
ANCILLARIES ONLY	N		

INVESTIGATOR	DEPARTMENT	NON-HOST INSTITUTION: STATE, COUNTRY
MAYER, BRUCE J PHD	GENETICS & DEV BIOLOGY	
KURTZMAN, SCOTT MD	Surgery	
ZARFOS, KRISTEN MD	Surgery	

SUBPROJECT DESCRIPTION:

Histologic analysis of breast cancer and lymph nodes does not accurately predict the likelihood of distant metastases. Novel molecular diagnostic markers, which can classify tumors based on their biological properties, are likely to provide useful prognostic information that can identify patients who will benefit from adjuvant treatment. SH2 profiling is a novel method that can provide detailed information about the global tyrosine phosphorylation state of tumor cells. We will use a novel variant of SH2 profiling technology to screen archived breast cancer specimens, to test whether this method can be used as a basis for classification and whether such SH2-based classifications have prognostic value. Formalin-fixed, paraffin-embedded samples of invasive breast carcinoma will be tested for binding to a panel of Src Homology 2 (SH2) domains. The pattern of SH2 binding to each tumor (whether strongly positive, weakly positive, or negative) will be scored for each SH2 domain probe. This SH2 profile data will then be compared with patient outcomes data (recurrence and mortality) and statistical analyses will be performed to determine if there is a significant correlation between SH2 binding pattern and patient outcomes.

SUBPROJECT PROGRESS:

This study has not enrolled any patients in the last two years and therefore will not be pursued affective November 2006. However; after an appropriate recruitment strategy is devised, the Principal Investigator may resurrect this project through the GCRC.

SPID:	0457	PROTOCOL:	457	TYPE:	RESEARCH	
SHORT TITLE:	Detrusor Overactivity					
LONG TITLE:	The Pathogenesis of Detrusor Overactivity					
AIDS:	N	TOTALS		A	B	D
		Inpatient		0	0	0
START DATE:	9/4/2002	Scatter Bed		0	0	0
Total # pts expected for entire study:	50	Outpatient		0	0	0
		Scatter RN Hours		0	0	0
		Offsite Visits		0	0	0
RESEARCH BIONUTRITION	N	MULTICENTER STUDY		Y		
INFORMATICS CORE	N	CLINICAL TRIAL		N		
BIostatistician	Y	CORE LAB		N		
ANCILLARIES ONLY	N					

INVESTIGATOR	DEPARTMENT	NON-HOST INSTITUTION: STATE, COUNTRY
KUCHEL, GEORGE A MD	CENTER ON AGING	

SUBPROJECT DESCRIPTION:

Urinary incontinence is prevalent and morbid in the elderly, and its associated costs exceed \$28 billion annually. Yet little is known about its most common cause, detrusor activity. Lack of basic knowledge severely limits the ability to devise sorely needed more effective interventions. This study is the fourth in a series, continuously funded by National Institutes of Health (NIH) over the past decade, which have proved that it is possible to perform invasive measurements of bladder function and structure in the frail elderly, safely and effectively. In 115 elderly subjects, blinded and prospective studies have documented a match between urodynamic function and detrusor ultrastructure. In every subject with detrusor overactivity (but in none without it), normal muscle cell junctions were largely replaced by new types of junctions, resembling gap junctions. Gap junctions normally abound only in electrically coupled smooth muscle, suggesting that in geriatric detrusor overactivity the normal mechanical cell coupling changes to an electrical one.

Our findings have been reproduced, substantiated longitudinally, corroborated by others, and seen in geriatric detrusor overactivity in every clinical setting. In addition, our preliminary data suggest that detrusor overactivity related to suprapontine lesion can be differentiated from detrusor overactivity due to other causes. However, 3 recent studies have raised the possibility that the pathophysiology of detrusor overactivity differs in younger adults. Moreover, specific changes seen by us in age-matched elderly controls suggest that aging itself may be associated with muscle cell de-differentiation, so setting the stage for geriatric detrusor overactivity.

The aim of this new study is to answer 4 important questions: 1) Do changes seen in elderly control subjects represent aging, or just previously undocumented features of normal bladder? 2) Is the correlation between altered cell junctions and detrusor overactivity really absent in younger individuals or just an artifact of study design? 3) Are the new junctions actually gap junctions? 4) Can detrusor overactivity associated with suprapontine lesion be differentiated from other types? We will address these issues in a blinded, prospective study of adults of all ages.

Using our proven urodynamic and biopsy techniques, we will compare bladder biopsies from 50 newly recruited adults with ages distributed over the range 21-64 years, with and without detrusor overactivity, to each other and to similar samples already acquired from 115 aged subjects. We will attempt to recruit equal numbers with and without a suprapontine upper motor neuron lesion. In 14 elderly subjects (>64 years) newly recruited for this study, molecular biology techniques will be used to test whether detrusor muscle with the new junctions expresses certain genes specific to gap junctions. By further clarifying the role of altered cell junctions, the study should provide valuable insights into the pathogenesis of detrusor overactivity and ultimately therapeutic strategies that will benefit millions of older Americans afflicted with this common morbid, and neglected condition.

SUBPROJECT PROGRESS:

We are working on a manuscript at this time.

SPID: 0459	PROTOCOL: 459	TYPE: RESEARCH
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SHORT TITLE:	Inhaled Nitric Oxide
LONG TITLE:	Inhaled Nitric Oxide for the Prevention of Chronic Lung Disease

AIDS:		TOTALS	A	B	D
	N	Inpatient	0	0	0
START DATE:	11/1/2002	Scatter Bed	0	0	0
Total # pts expected for entire study:	20	Outpatient	0	7	0
		Scatter RN Hours	0	0	0
		Offsite Visits	0	0	0

RESEARCH BIONUTRITION	N	MULTICENTER STUDY	Y
INFORMATICS CORE	Y	CLINICAL TRIAL	N
BIostatistician	N	CORE LAB	N
ANCILLARIES ONLY	N		

INVESTIGATOR	DEPARTMENT	NON-HOST INSTITUTION: STATE, COUNTRY
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PAPPAGALLO, MARIANN MD	Pediatrics	
KNOX, ISABELLA MD	Pediatrics	
ROSENKRANTZ, TED S MD	Pediatrics	
SANDERS, MARILYN MD	Pediatrics	
VIDWANS, ANIRUDDHA MD	Pediatrics	

SUBPROJECT DESCRIPTION:

Inhaled nitric oxide (iNO) therapy is a safe and effective treatment for term newborns with persistent pulmonary hypertension of the newborn and hypoxemic respiratory failure. However, little is known about the potential role of iNO in premature newborns with respiratory failure. The premature newborn is particularly susceptible to the adverse effects of ventilator-induced lung injury, oxygen toxicity, and lung inflammation which contribute to the development of chronic lung disease (CLD). Despite treatment with exogenous surfactant and steroids, CLD remains a major cause of morbidity and mortality in premature newborns. Moreover, there is increasing evidence that steroid treatment causes long-term adverse neurodevelopmental and cardiopulmonary sequelae.

Early clinical observations suggest that low-dose iNO improves oxygenation and decreases the need for mechanical ventilator support in the premature infant. In addition to its effects on gas exchange, recent laboratory and clinical observations suggest that iNO may also act as a lung-specific anti-inflammatory treatment and reduce the contribution of lung inflammation to the evolution of acute and chronic lung injury in premature infants.

SUBPROJECT PROGRESS:

There were a total of six patients enrolled at this site since initiation of this study. It is a multi-center study. Enrollment is complete and the study is now in the follow-up phase. One patient was lost to follow-up so we are following a total of five patients. There are no changes anticipated to the protocol nor have there been any unexpected safety concerns identified. -no interim data available. There have been no publications submitted from this site.

SPID: 0461 **PROTOCOL:** 461 **TYPE:** RESEARCH

SHORT TITLE: Effects of Oral Estradiol Therapy on Osteoclastogenesis

LONG TITLE: The Acute Effects of Oral Estradiol Therapy on Osteoclastogenesis in Hypogonadal Older Men and Women:
A Pilot Study

AIDS:	N	TOTALS	A	B	D
		Inpatient	0	0	0
START DATE:	3/6/2003	Scatter Bed	0	0	0
Total # pts expected for entire study:	124	Outpatient	9	0	0
		Scatter RN Hours	0	0	0
		Offsite Visits	0	0	0

RESEARCH BIONUTRITION	N	MULTICENTER STUDY	N
INFORMATICS CORE	Y	CLINICAL TRIAL	N
BIostatistician	N	CORE LAB	Y
ANCILLARIES ONLY	N		

INVESTIGATOR	DEPARTMENT	NON-HOST INSTITUTION: STATE, COUNTRY
TAXEL, PAMELA MD	Medicine	
LORENZO, JOSEPH A MD	MEDICINE	
RAISZ, LAWRENCE G MD	Medicine/Endocrinology	

SUBPROJECT DESCRIPTION:

Our understanding of the mechanisms by which estrogens regulate bone cells are incomplete. This process is important because estrogen loss by women after menopause and probably in hypogonadal men produces a relatively rapid decrease in bone mass and predisposes susceptible individuals to the development of the disease osteoporosis. This translational project is the result of a collaboration between basic and clinical scientists at the University of Connecticut Health Center (UCHC) whose work focuses on the identification of the mechanisms by which human beings develop the disease osteoporosis. Our specific goal in this pilot project is to examine the differences in cellular and molecular changes that occur in the bone marrow of sex steroid-replete and deficient older men and postmenopausal women in response to estrogen, as preliminary data in mice demonstrates the importance of this hormone.

In preliminary work we have found that ovariectomy in mice is rapidly followed by an increase in the ability of bone marrow cells to differentiate into osteoclasts, the cells that mediate bone resorption. This finding suggests that regulates the ability of hematopoietic precursor cells to differentiate into osteoclasts, a process that has not been adequately examined. Since increased rates of bone resorption appear to be the earliest known effects of estrogen withdrawal on the human skeleton, a better understanding of this process may lead to more effective therapies for the treatment of osteoporosis in both men and women.

Specific Aim 1: Examine the osteoclastogenic potential of each of these three groups of older men by evaluation of bone marrow aspirates both before and after treatment with Estrogen (E2).

Specific Aim 2: Examine parameters of B-lymphocyte lineage development and osteoclast formation in cells from bone marrow including markers of B-lymphocyte lineage development, and the percentage of early and mature B-lymphocytes in the bone marrow before and after E2 treatment. These studies will also evaluate the ability of fractionated (CD19+ and CD19-) bone marrow cells to form osteoclasts-like cells in vitro with and without treatment with receptor activator of NF-kappa B-ligand (RANKL) and monocyte- colony stimulating factor (M-CSF).

Specific Aim 3: Examine the expression in the bone marrow of factors known to influence osteoclast formation including messenger ribonucleic acid (RNA) for RANKL, receptor activator of NF-kappa B (RANK), osteoprotegerin (OPG), M-CSF and the M-CSF receptor (c-Fms). We will also measure protein levels of RANK and c-Fms by flow cytometry.

SUBPROJECT PROGRESS:

This study has resumed as we now have the laboratory personnel to conduct this study. We have had 5 more subjects in the current reporting period. In the first two of these subjects we verified that we were indeed making osteoclasts by demonstrating the ability of the cultured cells to form resorption pits. The next 3 subjects are now in the interventional protocol in order to extend out pilot data on the first 8 subjects. We have recently submitted a manuscript on these data. We have acknowledged the GCRG in the manuscript. Estradiol Rapidly Inhibits Osteoclastogenesis and RANKL expression in bone marrow cultures in Postmenopausal Women: A Pilot Study *P. Taxel,1 *H. Kaneko,2 S-K. Lee,1 H. L. Aguila,1 L. G. Raisz,1J. A. Lorenzo1 ABSTRACT Introduction: Estrogen (E2) deficiency at menopause increases osteoclast (OCL) formation and bone resorption, predisposing women to osteoporosis. We examined Receptor Activator of NF-kappa B-ligand (RANKL) expression and in vitro OCL formation in cultured bone marrow cells

from 8 postmenopausal women before and after 3 weeks of E2 therapy and 3 untreated premenopausal women.

Methods: Tartrate Resistant Acid Phosphatase (TRAP) staining and resorption pit assay determined OCL number and function. Flow cytometry measured the distribution of marrow cell types and expression of RANKL in the macrophage-enriched fraction (R1) and a lymphocyte-enriched fraction (R2). Results: RANKL (3-100 ng/ml) produced a dose-dependent increase in in vitro OC formation and E2 therapy significantly ($p < 0.01$) inhibited OCL formation by 33 to 50%. A small proportion of marrow cells bound anti-RANKL Ab (0.2-4.3%). There was no effect of E2 on the percentage of cells binding the anti-RANKL Ab in the R1 fraction. In the R2 fraction E2 treatment decreased the percentage of cells binding anti-RANKL Ab by 68 to 91% ($p < 0.01$). Conclusion: Three weeks of E2 treatment had a dual action. It inhibited the ability of hematopoietic cells to form OCLs in response to RANKL, and decreased the production of RANKL in cells of the bone marrow. The observed changes in the osteoclastic potential of bone marrow cells are likely involved in the ability of E2 to regulate bone mass and influence the development of osteoporosis.

SPID: 0466	PROTOCOL: 466	TYPE: RESEARCH
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SHORT TITLE: Nicotine Replacement Treatment (SNAP) Nicotine Replacement

LONG TITLE: Nicotine Replacement Treatment for Pregnant Smokers

AIDS:	N	TOTALS	A	B	D
		Inpatient	0	0	0
START DATE:	12/2/2002	Scatter Bed	0	0	0
Total # pts expected for entire study:	266	Outpatient	343	0	0
		Scatter RN Hours	0	0	0
		Offsite Visits	0	0	0

RESEARCH BIONUTRITION	N	MULTICENTER STUDY	Y	
INFORMATICS CORE	Y	CLINICAL TRIAL	Y	Phase III
BIostatistician	Y	CORE LAB	Y	
ANCILLARIES ONLY	N			

INVESTIGATOR	DEPARTMENT	NON-HOST INSTITUTION: STATE, COUNTRY
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ONCKEN, CHERYL MD	Medicine	
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SUBPROJECT DESCRIPTION:

Although medications are first-line treatment for smoking cessation in adults (1), and 30-40% of obstetricians prescribe or recommend over-the-counter nicotine replacement therapies for smoking cessation during pregnancy (2,3), little information on the efficacy or safety of these products is available for pregnant smokers. We propose a randomized, placebo-controlled, clinical trial to assess the utility of nicotine gum for smoking cessation during pregnancy. Subjects for this trial will be recruited from a large prenatal clinic in Hartford, Connecticut. This clinic serves an indigent population with a smoking rate of 29%. In addition to testing the efficacy and safety of the intervention, we will examine predictors of response among the women and we will conduct an analysis of maternal genetic factors that can augment the adverse effects of smoking on the fetus.

The specific aims of this study are: to compare the efficacy of nicotine gum or a matching placebo for smoking cessation among pregnant smokers; to examine whether nicotine versus placebo gum reduces the number of cigarettes smoked per day by pregnant smoker; to evaluate the safety of nicotine gum for smoking cessation during pregnancy. Specifically, we will compare nicotine gum with placebo on overall nicotine exposure (as measured by salivary cotinine), overall tobacco exposure (as measured by exhaled carbon monoxide and urinary alkaloids), and birth weight at the time of delivery; to identify factors that determine which subjects benefit the most from the use of nicotine replacement therapy for smoking cessation during pregnancy; and to examine the interaction between maternal smoking and allelic variation at two genetic loci (CYP1A1 and GSTT1) on birth weight in a racially diverse sample of pregnant smokers. As an exploratory aim we will also evaluate the interaction between smoking cessation and allele variations of other selected phase I and II genes of drug metabolism on birth weight.

SUBPROJECT PROGRESS:

Since the initiation of the study we have had approximately 33 subjects enrolled in the pilot study and approximately 170 subjects enrolled in the randomized trial. We are in the process of validating the final enrollment numbers. Due to double entries in our tracking system, this may be somewhat of an overestimate. The study was closed to enrollment this last fall due to the recommendation of the Data Safety Monitoring Board (DSMB). Although there were no safety concerns, and despite the fact that the overall efficacy was approximately double in the treatment versus the control group, the overall quit rates were so low that to determine statistical significance one would need a much larger number of subjects than we proposed and is feasible. Consequently we closed the trial, but will continue with genetics recruitment. No publications to date.

SPID: 0467 **PROTOCOL:** 467 **TYPE:** RESEARCH

SHORT TITLE: Smoking Cessation
LONG TITLE: Smoking Cessation and Bone Remodeling in Adolescents

AIDS:	N	TOTALS	A	B	D
		Inpatient	0	0	0
START DATE:	10/23/2002	Scatter Bed	0	0	0
Total # pts expected for entire study:	120	Outpatient	0	0	0
		Scatter RN Hours	0	0	0
		Offsite Visits	0	0	0

RESEARCH BIONUTRITION	N	MULTICENTER STUDY	N
INFORMATICS CORE	N	CLINICAL TRIAL	N
BIostatistician	Y	CORE LAB	N
ANCILLARIES ONLY	N		

INVESTIGATOR	DEPARTMENT	NON-HOST INSTITUTION: STATE, COUNTRY
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ONCKEN, CHERYL MD Medicine

SUBPROJECT DESCRIPTION:

Adolescent smoking rates are higher than among adults. High teenage smoking rates are due to increased smoking initiation rates in young persons and low success rates of adolescent smoking treatment programs. Low success rates may result from treatments focusing on the long-term health risks of smoking, and adolescents being less concerned about these risks. In order to optimize smoking treatment in adolescents, the Centers for Disease Control recommends that programs emphasize the immediate health benefits of smoking cessation (i.e., improved lung function, whiter teeth, better smelling breath). Unfortunately, these health benefits may not be meaningful enough for adolescents to quit smoking. Other potentially persuasive benefits of smoking cessation, such as the effects of smoking cessation on bone remodeling, have yet to be fully explored. This information holds promise to be beneficial for smoking treatment (especially in adolescent boys) if it can be presented in terms of maximal bone strength and height potential. It also may provide useful information on the effects of smoking cessation for osteoporosis prevention and treatment, which may motivate the public health community to invest more dollars to combat the epidemic of teenage smoking. The specific aims of this study are to determine the effects of smoking cessation on biochemical markers of bone turnover in adolescents and to elucidate the potential mechanisms by which smoking could affect bone turnover by measuring plasma cotinine concentrations and hormone profiles.

SUBPROJECT PROGRESS:

All subjects have been enrolled. There have been no new subjects enrolled in the report period. We plan to analyze the data this year. No unexpected safety concerns--this is a low risk study. No publications to date.

SPID: 0468 **PROTOCOL:** 468 **TYPE:** RESEARCH

SHORT TITLE: Genetics of Alcohol Dependence

LONG TITLE: Genetics of Alcohol Dependence (Family Controlled Linkage Disequilibrium Studies in Alcoholism)

AIDS:	N	TOTALS	A	B	D
		Inpatient	0	0	0
START DATE:	10/23/2002	Scatter Bed	0	0	0
Total # pts expected for entire study:	900	Outpatient	142	0	0
		Scatter RN Hours	0	0	0
		Offsite Visits	0	0	0

RESEARCH BIONUTRITION	N	MULTICENTER STUDY	N
INFORMATICS CORE	N	CLINICAL TRIAL	N
BIostatistician	N	CORE LAB	Y
ANCILLARIES ONLY	N		

INVESTIGATOR	DEPARTMENT	NON-HOST INSTITUTION: STATE, COUNTRY
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KRANZLER, HENRY R MD	PSYCHIATRY	
CONNER, TAMLIN PHD	Psychiatry	
DRAZINIC, CAROLYN MD	Psychiatry	

SUBPROJECT DESCRIPTION:

The only specific genes known to affect risk for alcohol dependence (AD) are some of those coding enzymes important for ethanol metabolism. Promising linkage regions have been identified in two genome scans, but for genetically heterogeneous disorders (like AD), strategies that rely purely on linkage in the absence of disequilibrium for gene localization are likely to be insufficient for gene discovery. Linkage disequilibrium (LD) studies, using methods such as the transmission-disequilibrium test (TDT) (Spielman et al., 1993), provide a possible solution, and delineation of the properties of these methods has been the subject of many recent studies. These methods address the gene localization shortcomings of linkage designs.

LD studies are complementary to conventional linkage approaches, but to be applied, they require specialized clinical materials, collected under rigorous ascertainment conditions. Our proposed sample will be recruited through affected probands and not conditioned on affection of more than one family member (although making use of multiple affecteds when available), and will be more representative of alcoholism in the target population than samples recruited based on multiple affecteds in each family. We will increase our chance of success by applying a novel approach to sample collection: we will specifically target the African-American (AA) population, a recently admixed population.

Extensive regions of LD in AA populations have been demonstrated by Lautenberger et al. (2000); our data support LD to >7 cM in AAs recruited in Connecticut. While most project resources will be allocated to sample collection, we will also study a series of markers mapped to regions showing statistically significant linkage to AD in prior studies, and we will seek new markers in these regions and candidate loci.

SUBPROJECT PROGRESS:

We recruited 181 participants for this study between 3/31/06 and 4/1/07. We have recruited a total of 964 subjects (261 control and 703 affected individuals) in the study. Health Insurance Portability and Accountability Act (HIPAA) waiver for phone screening phase only was submitted and approved. There was a change to the phone script to reflect change in payment (previously (Institutional Review Board) IRB approved) from \$75 to \$100; also an unnecessary section of the phone screen was removed. We also increased our enrollment to a maximum of 1200 participants to provide adequate statistical power to conduct the analyses proposed in the application. As of 4/30/07 this study will be closed to enrollment. The following articles cite the GCRC: Luo X, Kranzler HR, Lappalainen J, Yang B, Gelernter J. ADH4 gene variation is associated with alcohol and drug dependence in European Americans: Results from HWD tests and case-control association studies, *Neuropsychopharmacology*, 31:1085-1095, 2006. Luo X, Kranzler HR, Zuo L, Lappalainen J, Yang B, Gelernter J. ADH4 gene variation is associated with alcohol dependence and drug dependence in European Americans: Results from HWD tests and case-control association studies. *Neuropsychopharmacology*, 31:1085-1095, 2006. Luo X, Kranzler HR, Zuo L, Wang S, Lappalainen J, Schork NJ, Gelernter J: Diplotype trend regression (DTR) analysis of the ADH gene cluster and ALDH2 gene: Multiple significant associations for alcohol and drug dependence. *American Journal of Human Genetics*, 78:973-987, 2006. Zhang H, Kranzler HR, Lappalainen J, Luo X, Yang BZ, Krupitsky E, Pchelina S, Zvartau E, Gelernter J: Association between two 'b5-opioid receptor gene (OPRM1) haplotype blocks and drug or alcohol dependence. *Human Molecular*

Genetics, 15:807-819, 2006. Herman AI, Kranzler HR, Cubells JF, Gelernter J, Covault J: Association study of the CNR1 gene exon 3 alternative promoter region polymorphisms and substance dependence. *American Journal of Medical Genetics*, 141B:499-503, 2006.

Lappalainen J, Krupitsky E, Kranzler HR, Luo X, Remizov M, Pchelina S, Taraskina A, Zvartau E, Räsänen P, Makikyro T, Somberg LK, Krystal JH, Stein MB, Gelernter J: Mutation screen of the GAD2 gene and association study of alcoholism in three populations. *American Journal of Medical Genetics*, 2006 Oct 10; [Epub ahead of print].

Zhang H, Kranzler HR, Yang B, Luo X, Gelernter G: The OPRD1 and OPRK1 loci in alcohol or drug dependence: OPRD1 variation modulates substance dependence risk. *Molecular Psychiatry*, in press.

Covault J, Gelernter J, Jensen K, Anton R, Kranzler HR. Markers in the 5'Region of GABRG1 associate to alcohol dependence and are in linkage disequilibrium with markers in the adjacent GABRA2 gene, *Neuropsychopharmacology*, in press.

Zuo L, Kranzler HR, Luo X, Covault J, Gelernter J: CNR1 variation modulates risk for drug and alcohol dependence. *Biological Psychiatry*, in press.

SPID: 0469 **PROTOCOL:** 469 **TYPE:** RESEARCH

SHORT TITLE: Lower-Cost HIV Contingency Management

LONG TITLE: Lower-Cost (Human Immunodeficiency Virus) HIV Contingency Management in a Group Setting

AIDS:	Y	TOTALS	A	B	D
		Inpatient	0	0	0
START DATE:	10/24/2002	Scatter Bed	0	0	0
Total # pts expected for entire study:	172	Outpatient	13	0	0
		Scatter RN Hours	0	0	0
		Offsite Visits	811	0	0

RESEARCH BIONUTRITION	N	MULTICENTER STUDY	N
INFORMATICS CORE	N	CLINICAL TRIAL	N
BIostatistician	N	CORE LAB	N
ANCILLARIES ONLY	N		

INVESTIGATOR	DEPARTMENT	NON-HOST INSTITUTION: STATE, COUNTRY
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PETRY, NANCY M PHD	PSYCHIATRY	
CARROLL, KATHLEEN M PHD	MEDICINE	YALE UNIVERSITY, CT USA
DIECKHAUS, KEVIN MD	Medicine/Infectious Diseases	

SUBPROJECT DESCRIPTION:

Voucher contingency management (CM) interventions are efficacious in enhancing retention in treatment and reducing drug use, but they have not been implemented widely in community-based programs. A lower-cost CM procedure, that provides opportunities to win prizes ranging in value from \$1 to \$100, shows efficacy in retaining substance abusers in an HIV drop-in center (Petry et al., 2001), as well as in reducing substance use in traditional, community-based treatment programs (Petry et al., 2000; Petry & Martin, in press).

The purpose of this study is to evaluate the efficacy of this CM technique in enhancing attendance, reducing drug use, and improving health among clients attending (Human Immunodeficiency Virus) HIV drop-in centers. Specifically, 172 clients will be randomly assigned to one of two 6-month treatment conditions: standard 12-step oriented group treatment, or CM group treatment. In the CM group, clients earn the chance to win prizes for submitting clean urine specimens and for complying with steps toward their treatment goals. Activities related to improving health will be emphasized, such as attending medical appointments, recording daily medication consumption, getting prescriptions filled, and attending medication adherence support groups. Group attendance, drug use, medical problems and services received, and risky drug use and sexual behaviors will be measured pre-treatment, at months 3 and 6, and at 9- and 12-month follow-up evaluations.

Compared to the control condition, we expect that those assigned to the CM condition will show greater retention in treatment, reductions in drug use, improvements in health, and decreases in risk behaviors. This study represents an important extension of our previous and ongoing work in low-cost CM in that it involves a specific population of substance abusers (HIV-positive), expands our work to non-traditional, community-based settings (drop-in centers), and implements the CM approach in a group (rather than individual) format.

SUBPROJECT PROGRESS:

Total Enrollment: 172; Past Year Enrollment: 38; No changes in recruitment plans are needed; No unexpected safety concerns have occurred; Interim data and outcomes are not available; No changes were made to the protocol and none are anticipated; No publications since previous annual report.

SPID: 0470 **PROTOCOL:** 470 **TYPE:** RESEARCH

SHORT TITLE: Cortisol Response to Naloxone
LONG TITLE: Examination of the Dose Effect of a Functional Polymorphism at the Mu-Opioid Receptor Locus (OPRM1) and Hypothalamic-Pituitary-Adrenal (HPA) Axis Activation

AIDS:	N	TOTALS	A	B	D
			Inpatient	0	0
START DATE: 10/17/2002		Scatter Bed	0	0	0
			Total # pts expected for entire study: 20	Outpatient	0
		Scatter RN Hours	0	0	0
		Offsite Visits	0	0	0

RESEARCH BIONUTRITION	N	MULTICENTER STUDY	N	
INFORMATICS CORE	N	CLINICAL TRIAL	Y	Phase II-III
BIostatistician	Y	CORE LAB	N	
ANCILLARIES ONLY	N			

INVESTIGATOR	DEPARTMENT	NON-HOST INSTITUTION: STATE, COUNTRY
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COVAULT, JONATHAN MD, PHD	Psychiatry	
DEMARTINIS, NICHOLAS MD	Psychiatry	
KRANZLER, HENRY R MD	PSYCHIATRY	

SUBPROJECT DESCRIPTION:

Individuals with the variant form of the A118G (Asn40Asp) polymorphism in exon 1 of the m-opioid receptor gene (genetic locus OPRM1) appear to have a greater cortisol response to opioid blockade after naloxone administration. This study will examine whether there is a dose-effect relationship between the presence of the variant Asp40 allele and HPA axis activation by opioid blockade. Additionally, we will examine the relationship between Asn40Asp alleles and measures of anxiety, distress, and cardiovascular reactivity following the naloxone challenge.

METHODS: The study will employ a balanced, within-subject design involving two test days over a period of 3-7 days to examine cortisol response to intravenous naloxone (125 mcg/kg) or placebo in 36 healthy subjects (12 subjects in each of the three genotypic groups: Asn40 homozygotes, heterozygotes and Asp40 homozygotes). Deoxyribonucleic acid (DNA), isolated from whole blood will be POLYmerase chain reaction (PCR)-amplified and genotyped using artificial restriction sites, restriction enzyme digestion and agarose gel size fractionation. Plasma cortisol will be measured at 15-minute intervals over 120 minutes post infusion.

SUBPROJECT PROGRESS:

The study has been closed for enrollment since November 2005, the last subject ended participation in December 2005. No subjects were enrolled during the most recent grant year 13. Our final completion number (30 subjects completed on the 2 full lab sessions, 43 total enrolled) fell 20% short of our goal of 36 subjects. There were a few minor changes to the protocol during this report period. Huiping Zhang, Xingguang Luo, and Joel Gelernter were added to the study as co-investigators. While the study data was being verified for analysis, two errors were noticed that should have been reported at continuation as minor protocol deviations. In verifying the data, it was noticed that subject # 470-004 was enrolled outside of the age range of 18-30; this person was enrolled at age 35. Subject # 470-024 had the lab sessions scheduled 2 days apart versus 3-7 days apart, as stated on the study protocol. The enrollment of subject # 470-004 took place in 2003, and the enrollment of subject # 470-024 took place in 2004. Study personnel did not report these protocol deviations at continuation due to an oversight. There were no risks to subjects. An "Institutional Review Board" (IRB) Problem Report Form" and IRB addendum application was submitted to report this issue. Enrollment has ended and the study as been completed. Currently, the study is still under data analysis. A manuscript for publication - Hernandez-Avila, C., Covault, J., Wand, G., Zhang, H., Gelernter, J., and Kranzler, H.R. (2007) Population-Specific Effects of the Asn40Asp Polymorphism at the m-Opioid Receptor Locus (OPRM1) on HPA Axis Activation. - has recently been submitted to the journal Pharmacogenetics and Genomics. GCRC support including the grant number has been cited in the manuscript. We request the GCRC protocol remain active with the potential request for additional genotyping of the study participants at additional candidate loci related to regulation of the HPA axis.

SPID: 0471 **PROTOCOL:** 471 **TYPE:** RESEARCH

SHORT TITLE: Discovery and Assessment of Genetic and Environment
LONG TITLE: Discovery and Assessment of Genetic and Environmental Factors that Influence Severity and Progression of Hepato-Biliary Pancreatic Disease and Cancer μ -Opioid Receptor Polymorphism and Hypothalamic-Pituitary-Adrenal (HPA) Axis Activation

AIDS:	N	TOTALS	TOTALS		
			A	B	D
		Inpatient	0	0	0
START DATE:	11/4/2002	Scatter Bed	0	0	0
Total # pts expected for entire study:	1,000	Outpatient	23	0	0
		Scatter RN Hours	6	0	0
		Offsite Visits	0	0	0

RESEARCH BIONUTRITION	N	MULTICENTER STUDY	N
INFORMATICS CORE	Y	CLINICAL TRIAL	N
BIostatistician	N	CORE LAB	Y
ANCILLARIES ONLY	N		

INVESTIGATOR	DEPARTMENT	NON-HOST INSTITUTION: STATE, COUNTRY
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PROTIVA, PETR MD	Colon Cancer Prevention	
ABU-HASABALLAH, KHAMIS PHD	Psychiatry	
COVAULT, JONATHAN MD, PHD	Psychiatry	

SUBPROJECT DESCRIPTION:

Host genetic, acquired factors and environmental influences affect the development, severity, progression, and outcome of many chronic diseases, including hepato-biliary-pancreatic diseases. To facilitate the discovery of new genetic factors that influence development or progression of chronic diseases, we need to develop tissue and Deoxyribonucleic acid (DNA) banks and correlate results of polymorphisms and mutational analyses (genotypes) with patient and clinical characteristics (phenotypes). To provide the necessary databases for such studies, we need to build-up clinical databases and tissue and DNA banks. This project is designed to accomplish this for patients with hepato-biliary diseases seen at UConn who will be undergoing liver biopsies for reasons unrelated to this study. We expect the database and specimen repository thus developed will allow us to perform important and informative new analyses, and will form the basis for new grant and contract applications in the future. It will serve as a paradigm for other studies in other diseases and disorders. The potential is great for studies of the kind. We need support from the GCRC cores in order to get these initiatives off to a successful start.

SUBPROJECT PROGRESS:

total enrollment = 142 enrollment 4/1/06 - 3/31/07 = 32 there are no changes to recruitment at this time there are no unexpected safety concerns at this time there have been no publications at this time.

SPID: 0477	PROTOCOL: 477	TYPE: RESEARCH
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SHORT TITLE: SH2 Profiling

LONG TITLE: Feasibility of Src Homology 2 (SH2) Profiling as a Molecular Diagnostic Tool for Patients with Hematological Malignancies

AIDS:	N	TOTALS	A	B	D
		Inpatient	0	0	0
START DATE:	12/10/2002	Scatter Bed	0	0	0
Total # pts expected for entire study:	40	Outpatient	1	0	0
		Scatter RN Hours	0	0	0
		Offsite Visits	0	0	0

RESEARCH BIONUTRITION	N	MULTICENTER STUDY	N
INFORMATICS CORE	Y	CLINICAL TRIAL	N
BIostatistician	N	CORE LAB	N
ANCILLARIES ONLY	N		

INVESTIGATOR	DEPARTMENT	NON-HOST INSTITUTION: STATE, COUNTRY
MAYER, BRUCE J PHD	GENETICS & DEV BIOLOGY	
BONA, ROBERT MD	Medicine/Hem-Onc	
LI, ZIHAI MD, PHD	Ctr for Immunotherapy	

SUBPROJECT DESCRIPTION:

There is a need for molecular diagnostic tools that will allow the classification of tumors beyond what is currently possible using standard techniques. Ideally, markers will be identified that will have prognostic value (correlate with response to particular treatments, for example). Expression profiling using Complementary Deoxyribonucleic acid (cDNA) microarrays is now being tested for this purpose, but is at present cumbersome, costly, and is unlikely to give any information about the molecular defects in the tumor cell. We are developing a novel molecular diagnostic technique based on the profile of proteins in a tumor sample that bind to certain protein domains known to play an important role in signal transduction. In preliminary experiments this technique can identify different binding profiles in similar tumor types, suggesting it may be a valuable molecular diagnostic tool. The resulting profiles may also be informative about the molecular defects in a particular tumor. We propose to test this technique on samples from hematopoietic malignancies available at the UConn Health Center to establish the feasibility of implementation on a larger scale. Ultimately, if the technique is sufficiently robust and reproducible, we will correlate profiling data with patient information to determine whether the interaction profiling provides information with prognostic value.

SUBPROJECT PROGRESS:

No patients were enrolled in the past year, and a total of 57 have been enrolled over the course of the study to date. New enrollment was not pursued in the past year because lab personnel were focusing on other immediate priorities. In the next year we plan to re-focus on obtaining new hematological malignancy samples, and plan to enlist a resident or fellow to help with recruitment. The GCRC study coordinator has been extremely helpful in maintaining coded databases of samples and clinical outcomes, and in helping with Institutional Review Board (IRB) issues and recruitment. We have a manuscript describing the use of our SH2 profiling method in press, and anticipate that a publication describing SH2 profiling of leukemia samples obtained through this study and through collaborations will be submitted within the next year.

SPID: 0478	PROTOCOL: 478	TYPE: RESEARCH
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SHORT TITLE:	Iron
LONG TITLE:	The Role of Iron, Hemochromatosis Gene (HFE) Mutations, and Polymorphisms of other Genes in Chronic Hepatitis C (CHC)

	AIDS:	N	TOTALS	A	B	D
			Inpatient	0	0	0
START DATE:		1/9/2003	Scatter Bed	0	0	0
Total # pts expected for entire study:		2,400	Outpatient	77	0	0
			Scatter RN Hours	0	0	0
			Offsite Visits	0	0	0

RESEARCH BIONUTRITION	N	MULTICENTER STUDY	Y
INFORMATICS CORE	Y	CLINICAL TRIAL	N
BIostatistician	N	CORE LAB	Y
ANCILLARIES ONLY	N		

INVESTIGATOR	DEPARTMENT	NON-HOST INSTITUTION: STATE, COUNTRY
PROTIVA, PETR MD	Colon Cancer Prevention	
COVAULT, JONATHAN MD, PHD	Psychiatry	
LAMBRECHT, RICHARD PHD	Pharmacology & Toxicology	
WALSH, STEPHEN J SCD	Ctr for Biostatistics	

SUBPROJECT DESCRIPTION:

The success of the human genome project provides the promise of a new era in understanding and modifying human disease. It seems both likely and feasible that, during the next generation, we will identify the major host genes and their genetic variations, which modulate susceptibility to and severity of disease and responsiveness to medical therapies. To translate this promise into reality will require careful clinical characterizations of different patient phenotypes, coupled with determination of genotypes (genetic variations), gene expression information Messenger Ribonucleic Acid (mRNA's by microarrays, etc.), and information about translation of mRNA's into proteins (proteomics). A few studies have already identified genotypes that predict with greatly improved accuracy susceptibility to chronic vascular or neoplastic diseases and/or severity and outcome of these diseases. This project will take full advantage of the samples and clinical data obtained through the landmark HALT-C Trial, in order to develop a similar body of knowledge for chronic hepatitis C (CHC).

The long-term goal of this program is to ascertain the major genetic variations that predispose patients to develop advanced CHC and/or lack of responsiveness to (Interferon) IFN-based treatment. We will concentrate our efforts on variations in selected genes, which in previous smaller studies, have been shown to predict severity of CHC and/or responsiveness to IFN treatment. Specifically, we will delineate the role of iron, HFE gene mutations, and/or polymorphisms in other selected genes or gene promoters on the production and progression of CHC. Our major hypotheses are that hepatic iron, mutations of the HFE gene associated with human leukocyte antigen (HLA)-linked hereditary hemochromatosis (HHC), and/or selected polymorphisms in other genes, are important host factors that influence the progression of chronic hepatitis C to cirrhosis, decompensation, and hepatocellular carcinoma and/or the response of CHC to IFN-based therapies.

The specific aims of this project are:

To determine whether there is a direct correlation between progression of chronic hepatitis C (i.e., the major endpoints of the HALT-C Trial) and hepatic or total body iron content and/or the presence of the HFE gene mutations (C282Y, H63D, S65C) associated with HHC;

To determine whether there are correlations between progression of chronic hepatitis C and polymorphisms of the angiotensinogen promoter (Ang-P), apolipoprotein E (apo-E) genotype, the interleukin-10 promoter (IL-10-P), microsomal epoxide hydrolase (mEH), transforming growth factor-beta (TGF), or the tumor necrosis factor-alpha promoter (TNF-P);

To explore whether there are significant interactions among mutations of HFE, polymorphisms of other genes, and patients' responses to therapy or long-term outcomes; and

To determine whether the frequencies of these genetic variations differ significantly among subjects in the HALT-C Trial vs other subjects with less advanced CHC, or control subjects without CHC, matched for age, sex, and ethnicity.

SUBPROJECT PROGRESS:

280 subjects entered 4/1/06 - 3/31/07 = 82 there are no changes to recruitment plans at this time there are no unexpected safety concerns at this time. Data collection is still going on and data analysis has not begun.

SPID:	0486	PROTOCOL:	486	TYPE:	RESEARCH	
SHORT TITLE:	Human Babesiosis					
LONG TITLE:	Emerging Health Burden of Human Babesiosis					
AIDS:	N	TOTALS		A	B	D
		Inpatient		0	0	0
START DATE:	7/9/2003	Scatter Bed		0	0	0
Total # pts expected for entire study:	2,500	Outpatient		0	0	0
		Scatter RN Hours		0	0	0
		Offsite Visits		0	0	0
RESEARCH BIONUTRITION	N	MULTICENTER STUDY		Y		
INFORMATICS CORE	Y	CLINICAL TRIAL		N		
BIostatistician	Y	CORE LAB		N		
ANCILLARIES ONLY	N					

INVESTIGATOR	DEPARTMENT	NON-HOST INSTITUTION: STATE, COUNTRY
KRAUSE, PETER MD	Pediatrics	
SPIELMAN, ANDREW SCD	TROPICAL PUBLIC HEALTH	HARVARD UNIVERSITY, MA USA
TELFORD, SAM R SCD	INFECTIOUS DISEASE/IMMUNOL	TUFTS UNIVERSITY, MA USA
WALSH, STEPHEN J SCD	Ctr for Biostatistics	

SUBPROJECT DESCRIPTION:

Human babesiosis has increasingly been recognized as a growing health threat in the northeastern United States just as Lyme disease, transmitted by the same Ixodes tick, was recognized a decade ago. We have found that the incidence of babesiosis may approach that of Lyme disease in certain endemic areas and that babesiosis may cause severe and even life-threatening illness in young adults, as well as in the elderly and immunosuppressed. The distribution of babesial infection, like that of Lyme disease, appears to be progressing northward and westward from islands located along the southern New England coast and the health burden of human babesial infection appears to be underestimated. Our objectives, therefore, are to determine whether babesial infection is disseminating inland, whether its emergence in the human population can be predicted at emerging sites by analyzing tick or mouse infection, whether the frequency of severe babesial illness is greater in all age groups than previously recognized and whether Lyme disease or co-morbid conditions account for the majority of severe episodes of babesial illness. In particular, we shall:

1. Determine whether the dissemination of the agent of human babesiosis follows that of Lyme disease in the vector and in rodent and human hosts across southern New England and New York.
2. Determine whether the proportion of *B. microti* and *B. burgdorferi* infections in vector ticks and reservoir mice predicts that in the local human population.
3. Determine whether the age-specific incidence of severe babesial illness is greater than previously recognized and whether Lyme disease or co-morbid conditions account for the most severe episodes of babesial illness.

We anticipate that this proposed body of work will provide a basis for understanding how the distribution and intensity of babesiosis and Lyme disease develops in a region and how the emergence of these infections ultimately affects public health.

SUBPROJECT PROGRESS:

Progress Report 486 (IRB# 03-058) Title: Emerging Burden of Human Babesiosis 4/1/2006-3/31/2007 This project was reorganized to become part of project 496 (Health Burden of Deer-Associated Zoonoses). Thus, the same Progress report for that project is listed below: 1. The number of subjects enrolled during the report period was 629. 2. The number of subjects enrolled since initiation of the study has been 2,297. 3. No changes in recruitment plans have been needed. 4. There have been no unexpected safety concerns. 5. Interim data and outcomes have been summarized in the papers and regional/national talks listed below. 6. There were no proposed changes made or anticipated in the protocol, however, a restructuring of this project was submitted to the GCRC in November, 2006 and was approved. A summary of the proposed change as submitted is as follows, Following discussions at the GCRC and

Connecticut Children's Medical Center (CCMC), it became apparent that administrative aspects of the research projects listed above should be reorganized to provide a more unified approach. The proposed change is to include the minor GCRC project (486) as a subset of the major GCRC project (496) and re title the new expanded major project as, "Health Burden of Deer-Associated Zoonoses." This more general title would reflect the incorporation of minor project activities into the new major project and is the same title used for these projects at CCMC. The specific aims and methods of the old major project would remain unchanged while specific aims and methods of the minor project would remain largely intact because of the overlap in objectives and methods of the major and minor projects." 7. Presentations at regional/national meetings Macuda M, Foppa M, Krause PJ. Lyme disease prevention behaviors on Block Island: Patterns and Predictors. American Public Health Association, Boston, MA, November, 2006. Krause PJ. Emerging tick-borne zoonoses: Lyme disease, babesiosis, human granulocytic ehrlichiosis. American Society for Microbiology, 41st Annual Regional Meeting, Albany, NY, November 3, 2006. Krause PJ. Monitored ID platform session and delivered featured talk, "Development of a novel vaccine for prevention of tick-borne infections." Eastern Society of Pediatric Research. Philadelphia, PA, March 10, 2007.

SPID: 0487 **PROTOCOL:** 487 **TYPE:** RESEARCH

SHORT TITLE: Radiation-Induced Oral Mucositis
LONG TITLE: Cyclooxygenase-2 (Cox2) Inhibition in Radiation-Induced Oral Mucositis

AIDS:	N	TOTALS	TOTALS		
			A	B	D
		Inpatient	0	0	0
START DATE:	1/16/2003	Scatter Bed	0	0	0
Total # pts expected for entire study:	10	Outpatient	0	74	0
		Scatter RN Hours	0	0	0
		Offsite Visits	0	0	0

RESEARCH BIONUTRITION	N	MULTICENTER STUDY	N
INFORMATICS CORE	Y	CLINICAL TRIAL	N
BIostatistician	N	CORE LAB	Y
ANCILLARIES ONLY	N		

INVESTIGATOR	DEPARTMENT	NON-HOST INSTITUTION: STATE, COUNTRY
LALLA, RAJESH V BDS, PHD	ORAL DIAGNOSIS	
DAMATO, KATHRYN L MS	Oral Diagnosis	
DANNENBERG, ANDREW J MD	MEDICINE/GASTROENTEROL OGY	CORNELL UNIVERSITY, NY USA
DOWSETT, ROBERT J MD	Radiation Oncology	
HEGDE, UPENDRA MD	Medicine	
PETERSON, DOUGLAS DMD, PHD	Oral Diagnostics	
SONIS, STEPHEN T DMD, DMSC	ORAL & MAXILLOFACIAL SURGE	DANA FARBER CANCER INSTITUTE, MA USA

SUBPROJECT DESCRIPTION:

Oral mucositis refers to inflammatory, erythematous, erosive or ulcerative lesions of the oral mucosa seen in 60-90% of patients undergoing radiation therapy for head and neck cancer to fields involving the oral cavity. These lesions are painful, compromise nutrition and become secondarily infected. Hospitalization is required for pain control and nutritional support in approximately 15% of cases. Further, severe oral mucositis can necessitate interruptions in radiation therapy thus compromising cancer therapy. No agent is currently available to prevent oral mucositis or reduce its severity.

Available evidence implicates inflammatory responses to radiation therapy and to products of colonizing microorganisms in the pathogenesis of oral mucositis. The use of anti-inflammatory agents in oral mucositis has not been well-studied. However, the limited available data using non-steroidal anti-inflammatory drugs (NSAIDs) indicates that this is a promising approach. The use of celecoxib, a selective Cyclooxygenase-2 (COX-2) inhibitor, in radiation-induced oral mucositis has not been previously studied. Celecoxib offers several potential advantages in this setting as compared to conventional NSAIDs.

This pilot study is intended to generate preliminary data in preparation for submission to extramural funding sources. This randomized, double-blind, placebo-controlled pilot study will evaluate celecoxib in ten subjects at high risk for developing radiation-induced oral mucositis. Subjects will be randomized to 200 mg bid celecoxib or placebo (both by mouth) in a 1:1 ratio. They will be asked to use the study medication daily starting 5 days before the first day of radiation therapy until 3 days after the end of radiation therapy. The primary endpoint will be the investigator's evaluation of severity of oral mucositis using the Oral Mucositis Assessment Scale (OMAS). OMAS scores will be compared between the two groups to assess the impact of celecoxib on mucosal injury. The secondary endpoint will be evaluation of pain severity using the severity subscale of the Brief Pain Inventory. Additional assessments will include evaluation of 1. medications used for pain management 2. normalcy of diet 3. type, dose, duration and fields of radiation therapy and 4. mucosal injury using the World Health Organization (WHO) and Common Toxicity Criteria (CTC) mucositis scales.

Further, 2 mm punch biopsies of the oral mucosa will be obtained from consenting subjects in both groups at four time-points. Levels of selected enzymes, prostanoids and receptors involved in the cyclooxygenase pathway will be measured. In addition, a 10 ml blood sample will be obtained from subjects in both groups at four time-points. These blood samples will be used to measure levels of selected prostanoids generated via the cyclooxygenase pathway and of selected cytokines that induce COX-2 expression.

Comparison between the two groups will allow assessment of the role of the cyclooxygenase pathway in radiation mucositis and the impact of celecoxib. Correlations will be examined between levels of prostaglandins whose synthesis is mediated by COX-2 and mucosal injury and pain in radiation-induced oral mucositis.

This line of research could lead to the development of an agent to prevent or reduce the severity of oral mucositis. This would substantially decrease morbidity in these patients. In addition, it may also improve patient prognosis by avoiding breaks in cancer therapy.

SUBPROJECT PROGRESS:

Number of subjects enrolling during the report period: 3 and since initiation of the study: 10 - Any changes in recruitment plans that might be needed: None - Unexpected safety concerns and their resolution: None - Interim data and outcomes if appropriate: None - Any proposed changes made or anticipated in the protocol: Currently, only patients who receive head and neck radiation therapy with concurrent chemotherapy are eligible for the study. We have submitted a protocol modification request to Institutional Review Board(IRB) to allow patients who are receiving head and neck radiation therapy without concurrent chemotherapy to also be eligible for the study. - Publications, indicating whether the GCRC was cited: None so far

SPID: 0492	PROTOCOL: 492	TYPE: RESEARCH
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SHORT TITLE:	Keloid Formation
LONG TITLE:	Molecular Mechanisms for Keloid Formation

	AIDS:	N	TOTALS			
				A	B	D
			Inpatient	0	0	0
START DATE:			Scatter Bed	0	0	0
Total # pts expected for entire study:		50	Outpatient	13	0	0
			Scatter RN Hours	0	0	0
			Offsite Visits	7	0	0

RESEARCH BIONUTRITION	N	MULTICENTER STUDY	Y
INFORMATICS CORE	N	CLINICAL TRIAL	N
BIostatistician	N	CORE LAB	Y
ANCILLARIES ONLY	N		

INVESTIGATOR	DEPARTMENT	NON-HOST INSTITUTION: STATE, COUNTRY
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REICHENBERGER, ERNST PHD	Biostructure and Function	
GREENSTEIN, ROBERT MD	Pediatrics/Genetics	

SUBPROJECT DESCRIPTION:

The long-term goal of this study is to understand the molecular mechanisms of neof ormation of dermal tissue in fibrotic diseases. To achieve this goal we study hereditary keloid formation. Keloids are benign tumors of the skin or cornea caused by overactivity of fibroblasts during abnormal wound repair. The relatively large number of familial cases of keloid formation makes it possible to propose a genetic approach for the identification of a gene responsible for increased cell proliferation and extracellular matrix expression. We perform genome wide screening and linkage analysis of suitably large families afflicted with the autosomal dominant form of hereditary keloid formation. Subsequently we identify and analyze the chromosomal loci. We have identified possible disease gene loci and are now in the process of establishing high resolution maps of the keloid loci. Additional families need to be identified and recruited to verify and further characterize the loci. These families will be tested for co-localization. Suitable families that do not co-localize to an existing locus will be used for genome wide screening.

SUBPROJECT PROGRESS:

Total number of patients enrolled: 561 Current Year Enrollment: 186 Changes in recruitment plans: No changes needed. Unexpected safety concerns and their resolution: None Interim data and outcomes: We have enrolled 186 subjects during the reporting period. The GCRC-sponsored pilot project for recruitment in Nigeria has been highly successful. As a result of the support from the GCRC we were successful in receiving National Institute of Health (NIH) funding (RO1) for patient recruitment, mapping and linkage analysis for 5 years. Preliminary mapping is currently being performed with a pilot grant from the GCRC. Now the basis has been set for increased recruitment within the US and from Nigeria. The assistance of the GCRC Genetics Nurse Coordinator Ms. Victoria Odesina was essential for initiating the collaboration with Nigeria and will be equally important as we go forward with more intense recruitment schemes in Nigeria. Proposed changes made or anticipated in the protocol: None Publications: None.

SPID: 0494 **PROTOCOL:** 494 **TYPE:** RESEARCH

SHORT TITLE: Open Angle Glaucoma

LONG TITLE: Molecular Screening of Optineurin Gene in Patients with Adult-Onset Primary Open Angle Glaucoma

AIDS:	N	TOTALS	A	B	D
		Inpatient	0	0	0
START DATE:	2/26/2003	Scatter Bed	0	0	0
Total # pts expected for entire study:	250	Outpatient	0	0	0
		Scatter RN Hours	0	0	0
		Offsite Visits	0	0	0

RESEARCH BIONUTRITION	N	MULTICENTER STUDY	N
INFORMATICS CORE	N	CLINICAL TRIAL	N
BIostatistician	N	CORE LAB	Y
ANCILLARIES ONLY	N		

INVESTIGATOR	DEPARTMENT	NON-HOST INSTITUTION: STATE, COUNTRY
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SARFARAZI, MANSOOR PHD	Surgery	
REZAIE, TAYEBEH PHD	Surgery	

SUBPROJECT DESCRIPTION:

Glaucoma is an optic neuropathy that affects over 67 million people worldwide. This condition has broad clinical manifestation, possibly resulting from a significant genetic heterogeneity that exists within this group. Glaucoma is divided into many clinical subtypes, ranging from onset at birth to very late in life. The most common form, Primary Open Angle Glaucoma (POAG) has a prevalence of about 1% of a predominantly white population over 40 years of age. Several genetic loci have been identified for POAG but so far only mutations in Myocilin gene are predominantly reported in juvenile-onset and certain other adult-onset cases.

Recently, we identified a gene that is primarily involved in a subgroup of Adult-Onset POAG, commonly known as Normal Tension Glaucoma (NTG). This gene that we named Optineurin (for "Optic Neuropathy Inducing" protein; OPTN) is mutated in 16.7% of our hereditary NTG families. This gene maps to the GLC1E locus on 10p14 and has 13 coding exons that encodes for a protein with 577 amino acids (~66-kDa). Our OPTN protein studies showed co-localization with Golgi, secretion into aqueous humor and expression in many ocular and non-ocular tissues. Cloning of both mouse and monkey genes showed very similar patterns of Messenger Ribonucleic Acid (mRNA) and protein expression to human OPTN. It has also been shown by other investigators that OPTN interacts with Ad E3-14.7K, Huntingtin, TFIIIA, RAB8 and 2 other unknown kinases. Although existing evidence suggests that OPTN, through its interaction with other proteins may be utilizing TNF- α or Fas-Ligand pathways to mediate apoptosis, inflammation or vasoconstriction, as yet there is no clear indication on how OPTN mutations lead to either NTG or POAG. Therefore, as an initial step towards understanding the function of this gene and its protein products we propose to do the following: 1)-Screen a large number of glaucoma patients for OPTN mutations by SSCP/DHPLC and Automated Deoxyribonucleic acid (DNA) sequencing to establish a firm genotype/phenotype correlation. This specific aim will be done as a main part of this GCRC protocol. In a complementary study we plan to: 2)-Identify promoter, its transcription start points, binding sites, regulatory elements and to study its activity and expression patterns; 3)-Use OPTN as "bait" and search for new interacting proteins by a Yeast Two Hybrid System and to search for protein motifs that are important for OPTN function; 4) -Determine ultracellular localization of OPTN in normal and glaucomatous eyes by immunogold labeling; 5)-Study specific sites of localization of OPTN in normal and glaucomatous eyes by immunohistochemistry and to determine its potential differential expression patterns; and 6)-Use In Situ hybridization to study developmental expression patterns of OPTN in mouse embryos.

At the conclusion of this investigation, it is anticipated that our study will provide essential information that one day may contribute to the design of innovative drug intervention in this group of optic neuropathies.

SUBPROJECT PROGRESS:

During the last year limited number of individuals were recruited and processed by the GCRC Molecular Core Laboratory. The number of participating patients for this study has been much less than expected. There have been no changes to our active recruitment of these patients for this study. However, despite the fact that our clinical collaborators are still actively recruiting patients for this study, the numbers of patients that volunteered for this study have been limited. There has been no safety concern on any of the patients recruited during this time. The samples obtained and processed during the prior years will be analyzed together with other samples that have been processed in our laboratory. A joint analysis still needs to be completed. However, as expected we

have identified new Optineurin mutations in our samples. We have not made any changes to our protocols and anticipate that no changes are necessary to our current protocol for the upcoming year of this study.

SPID: 0495 **PROTOCOL:** 495 **TYPE:** RESEARCH

SHORT TITLE: Targeted Naltrexone for Problem Drinkers

LONG TITLE: Targeted Naltrexone for Problem Drinkers

AIDS:	N	TOTALS	A	B	D
			Inpatient	0	0
START DATE:	1/16/2003	Scatter Bed	0	0	0
Total # pts expected for entire study:	200	Outpatient	299	0	0
		Scatter RN Hours	0	0	0
		Offsite Visits	0	0	0

RESEARCH BIONUTRITION	N	MULTICENTER STUDY	N
INFORMATICS CORE	Y	CLINICAL TRIAL	N
BIostatistician	Y	CORE LAB	Y
ANCILLARIES ONLY	N		

INVESTIGATOR	DEPARTMENT	NON-HOST INSTITUTION: STATE, COUNTRY
KRANZLER, HENRY R MD	PSYCHIATRY	
ARMELI, STEPHEN R PHD	PSYCHIATRY	FAIRLEIGH-DICKINSON UNIV, NJ USA
COVAULT, JONATHAN MD, PHD	Psychiatry	
GELERNTER, JOEL E MD	PSYCHIATRY	YALE UNIVERSITY, CT USA
HERNANDEZ-AVILA, CARLOS MD	Psychiatry	
ONCKEN, CHERYL MD	Medicine	
TENNEN, HOWARD PHD	Community Medicine	

SUBPROJECT DESCRIPTION:

In the US, heavy drinking occurs commonly and is associated with a variety of alcohol-related problems. Available treatments for problem drinking have limited efficacy. This proposal is for a 12-week, placebo-controlled trial of naltrexone (50 mg orally) in 200 problem drinkers. Problem drinkers are those individuals whose drinking puts them at risk of a variety of psychosocial and medical problems, including alcohol dependence, but who are not physically dependent on alcohol. They are estimated to comprise up to 20% of the general population. The study will employ a factorial design in which the effects of medication (naltrexone vs. placebo), schedule of medication administration (i.e., daily vs. targeted), and the interaction of these factors on drinking behavior will be examined. Targeted administration refers to the use of medication to cope with anticipated high-risk drinking situations. The primary outcome measures will be drinking days and heavy drinking days. Secondary outcomes will include alcohol-related problems and biological measures of alcohol consumption (i.e., serum Gamma glutamyl transpeptidase (GGTP) and Carbohydrate-Deficient Transferrin CDT).

The study will extend the results of a recently completed 8-week trial of targeted naltrexone in early problem drinkers. That study showed a significant advantage of naltrexone over placebo on heavy drinking days and for targeted administration on daily drinking. The effects of targeted administration diminished substantially over time, apparently due to the schedule that was used for targeted medication administration.

In the proposed study, the targeted medication schedule has been modified, the sample size increased, the duration of treatment lengthened and a pharmacogenetic analysis added to examine the effect of allelic variation at candidate loci on the response to naltrexone. The daily monitoring of mood, desire to drink, perceived self-efficacy, and drinking behavior will make it possible to examine in depth the processes by which the study variables exert their effects.

Daily monitoring will be performed using automated telephone interviews, with in-person follow-up evaluations conducted at 3 and 6 months post-treatment to provide a measure of the durability of treatment effects. A pharmacogenetic analysis based on preliminary evidence showing that a functional polymorphism in the gene encoding the mu-opiate receptor (OPRM1) affects response to naltrexone will serve to explore an important source of variation in the response to naltrexone treatment. Exploratory analyses involving other the gene encoding the delta opioid receptor (OPRD1) will also be conducted. Careful evaluation of the study hypotheses will provide important information on the efficacy and mechanism of the effects of targeted naltrexone in problem drinkers. This study will allow us to model effects across multiple levels of analysis in an effort to apply novel genetic findings to understanding the psychopharmacological mechanisms underlying the therapeutic effects of naltrexone in problem

drinkers.

SUBPROJECT PROGRESS:

A total of 38 subjects were enrolled during the report period (a total of 184 since initiation of the study). As of 3/31/07, a total of 155 subjects had been randomized to receive treatment with either naltrexone or placebo and on either a daily or a targeted medication administration schedule. There are no changes needed in recruitment plans. There have been no unexpected safety concerns associated with this study. Final outcomes data are not available at this time. This study uses interactive voice response technology (IVR) for daily data collection, with support from the General Clinical Research Center (GCRC). The overall completion rate for IVR calls is 89.5% for days in study and 81.1% when all study days are included. There have been no recent publications associated with this study since data collection is ongoing. Changes made in the protocol during the report period include: 1) a Waiver of Consent for phone screening was obtained (as per Institutional Review Board(IRB) guidance on this issue), 2) modifications were made to the telephone script (to allow for referral of phone excludes to other active studies), and 3) we obtained IRB approval (in January 2007) to modify the study inclusion criteria to allow enrollment of individuals ages 66 through 70. Previously, the age range for inclusion was 18-65; the new age range is age 18 70, inclusive. This modification allows healthy older adults who meet all other study inclusion criteria to participate in the study. Subjects ages 66-70 generally can be as healthy as other subjects 65 and below. Inclusion of older adults involves a slight increase in risk to the subject, but careful screening prior to enrollment will preclude the randomization of subjects for whom participation is medically inappropriate. Given evidence in the literature that naltrexone is well tolerated by older adults, the risk of including subjects aged 66-70 is minimal. In conjunction with this modification, associated study materials were updated with the new age limit (protocol, telephone script, recruitment advertisements).

SPID: 0496	PROTOCOL: 496	TYPE: RESEARCH
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SHORT TITLE: Recurrent Lyme Disease

LONG TITLE: Recurrent Lyme Disease: Incidence, Pathogenesis and Clinical Outcome

	AIDS:	N	TOTALS	A	B	D
			Inpatient	0	0	0
START DATE:		5/15/2003	Scatter Bed	0	0	0
Total # pts expected for entire study:		5,000	Outpatient	268	0	0
			Scatter RN Hours	0	0	0
			Offsite Visits	0	0	0

RESEARCH BIONUTRITION	N	MULTICENTER STUDY	Y
INFORMATICS CORE	Y	CLINICAL TRIAL	N
BIostatistician	N	CORE LAB	Y
ANCILLARIES ONLY	N		

INVESTIGATOR	DEPARTMENT	NON-HOST INSTITUTION: STATE, COUNTRY
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KRAUSE, PETER MD	Pediatrics	
WALSH, STEPHEN J SCD	Ctr for Biostatistics	
WIKEL, STEPHEN PHD	Microbial Pathogenesis	

SUBPROJECT DESCRIPTION:

Lyme disease is the most frequently reported tick-borne infection in the United States. People who live in areas that are endemic for Lyme disease are often repeatedly exposed to bites of uninfected as well as infected Ixodes ticks and recurrent episodes of this infection have been reported. We found that about 14% of people experiencing Lyme disease on Block Island, Rhode Island suffered recurrent infection and that subsequent episodes of infection were associated with fewer symptoms than the initial infection. It is unclear whether a similar rate of recurrence and a milder clinical outcome during recurrent episodes occur at endemic mainland sites. It is also unclear what prevents the majority of people from experiencing either initial infection or recurrent infection when they are repeatedly exposed to *Borrelia burgdorferi*-infected ticks. Although immunity against the causative pathogen probably helps limit recurrence, immune responses directed against the tick vector also may help prevent initial and repeated infections. Our first two objectives are to compare frequency and clinical outcomes of recurrent Lyme disease on Block Island and at mainland sites in southern New England and New York. Our third objective is to examine relationships among immune responses to *I. scapularis* salivary gland proteins and protection against the development of primary and recurrent *B. burgdorferi* infections. In particular, we propose three specific aims.

1. Determine whether the frequencies of primary and recurrent Lyme disease differ among residents of Block Island, RI and of southern New England and New York.
2. Determine whether the acute symptoms of repeated episodes of Lyme disease are less severe than the initial episode of Lyme disease.
3. Determine whether immune factors directed against the tick *Ixodes scapularis* are protective against *B. burgdorferi* transmission and whether they correlate inversely with the incidence of primary and recurrent Lyme disease.

This proposed body of work will provide a basis for understanding the frequency and clinical outcome of recurrent Lyme disease and how immune factors directed against the tick vector may limit the incidence of recurrent Lyme disease and other tick-borne infections.

SUBPROJECT PROGRESS:

Progress Report 496 (IRB# 96-070A) Title: Health Burden of Deer-Associated Zoonoses 4/1/2006-3/31/2007 1. The number of subjects enrolled during the report period was 629. 2. The number of subjects enrolled since initiation of the study has been 2,297. 3. No changes in recruitment plans have been needed. 4. There have been no unexpected safety concerns. 5. Interim data and outcomes have been summarized in the papers and regional/national talks listed below. 6. There were no proposed changes made or anticipated in the protocol, however, a restructuring of this project was submitted to the GCRC in November, 2006 and was approved. A summary of the proposed change as submitted is as follows, Following discussions at the GCRC and Connecticut Children's Medical Center (CCMC), it became apparent that administrative aspects of the research projects listed above should be reorganized to provide a more unified approach. The proposed change is to include the minor GCRC project (486) as a subset of the major GCRC project (496) and re title the new expanded major project as, "Health Burden of Deer-Associated Zoonoses." This more general title would

reflect the incorporation of minor project activities into the new major project and is the same title used for these projects at CCMC. The specific aims and methods of the old major project would remain unchanged while specific aims and methods of the minor project would remain largely intact because of the overlap in objectives and methods of the major and minor projects." 7. Presentations at regional/national meetings Macuda M, Foppa M, Krause PJ. Lyme disease prevention behaviors on Block Island: Patterns and Predictors. American Public Health Association, Boston, MA, November, 2006. Krause PJ. Emerging tick-borne zoonoses: Lyme disease, babesiosis, human granulocytic ehrlichiosis. American Society for Microbiology, 41st Annual Regional Meeting, Albany, NY, November 3, 2006. Krause PJ. Monitored ID platform session and delivered featured talk, "Development of a novel vaccine for prevention of tick-borne infections." Eastern Society of Pediatric Research. Philadelphia, PA, March 10, 2007.

SPID: 0497	PROTOCOL: 497	TYPE: RESEARCH
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SHORT TITLE: TMD

LONG TITLE: Brief Focused Treatment for Temporomandibular Joint Dysfunction: Mechanisms of Action (TMD)

	AIDS:	N	TOTALS			
				A	B	D
			Inpatient	0	0	0
START DATE:			Scatter Bed	0	0	0
Total # pts expected for entire study:		112	Outpatient	130	0	0
			Scatter RN Hours	0	0	0
			Offsite Visits	0	0	0

RESEARCH BIONUTRITION	N	MULTICENTER STUDY	N
INFORMATICS CORE	Y	CLINICAL TRIAL	N
BIostatistician	N	CORE LAB	Y
ANCILLARIES ONLY	N		

INVESTIGATOR	DEPARTMENT	NON-HOST INSTITUTION: STATE, COUNTRY
LITT, MARK D PHD	BEHAVIORAL SCI & COMM HLTH	
KINGSBURY, JEFFREY DDS, MD	Oral & Maxillofacial Surge	
KREUTZER, DONALD L PHD	Pathology	
SHAFER, DAVID DMD	Behavioral Sci & Comm Hlth	

SUBPROJECT DESCRIPTION:

Temporomandibular joint dysfunction (TMD) is a widespread chronic pain condition. A number of psychosocial treatments for TMD have been developed that have been successful for a majority of patients. The mechanisms by which these treatments achieve their effects, however, are not well specified. The general goal of the current study is to evaluate the cognitive, behavioral, and physiological mechanisms of treatment to discover what accounts for treatment gains in this disorder. To do this we will deliver to patients a brief cognitive-behavioral treatment designed to maximize adaptive cognitions and behaviors, while periodically monitoring their pain, thoughts, feelings, and coping behaviors using an experience sampling paradigm. Specifically the aims are as follows:

- To evaluate the effects on TMD patients' pain and psychosocial functioning of a brief treatment that combines a standard splint therapy with a focused cognitive-behavioral program (STD+CBT) intended to maximize coping self-efficacy and minimize catastrophization in response to specific pain-related circumstances.
 - H1. It is hypothesized that patients exposed to the brief cognitive behavior treatment will have better outcomes than will a group of patients given a standard conservative treatment based on splint therapy without cognitive-behavioral treatment.
- To determine what situational factors and dispositional factors are predictive of general adaptation and pain perception following TMD treatment.
 - H2. It is expected that both dispositional factors, and situational factors measured four times daily, will play a role in predicting adaptation and pain following treatment.
- To determine specifically what moods, cognitions and coping behaviors are changed as a result of treatment.
 - H3. It is predicted that patients in the STD+CBT treatment will exhibit increased numbers of specific coping behaviors, improved mood, higher self-efficacy for pain control, and decreased frequency and intensity of catastrophization as measured in real time, as compared to STD patients, and that these changes will be associated with treatment outcome.
- To determine what effects treatment per se may have on measures of physiological stress and cell-mediated immunity.
 - H4. It is expected that, at the follow-up points, subjects in the STD+CBT group will have lower levels of plasma cortisol and lower levels of proinflammatory cytokines than will the STD subjects.
- To determine whether changes in treatment-related situational process variables such as self-efficacy are associated with changes in cortisol and cytokine levels, suggesting that psychosocial treatments act partly by altering HPA axis and cell-mediated inflammatory processes.
 - H5. It is hypothesized that changes in number of coping behaviors used and changes in situational self-efficacy and catastrophization will be correlated with changes in cortisol and cytokine levels from pre-to post-treatment.

The results may indicate what classes of variables need to be addressed to enhance treatment for TMD sufferers, and start to pinpoint the true active mechanisms accounting for improvement in TMD treatment. If these mechanisms can be successfully identified it would have implications for the development of more effective treatment programs for TMD and for related disorders.

SUBPROJECT PROGRESS:

88 subjects have been enrolled, 35 since last progress report. No changes in recruitment plans needed. There are no safety concerns. There are no interim data or outcomes available at this time. No changes are anticipated in the protocol. No publications have been prepared to date.

SPID: 0500	PROTOCOL: 500	TYPE: RESEARCH
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SHORT TITLE: PACTG 390

LONG TITLE: Pediatric AIDS Clinical Trial Group (PACTG) 390: A Phase II/III randomized, Open-Label Study of Combination Antiretroviral Regimens and Treatment-Switching Strategies in HIV Antiretroviral Naïve Children >30 Days and <18 Years of Age

AIDS:	Y	TOTALS	A	B	D
		Inpatient	0	0	0
START DATE:	7/1/2002	Scatter Bed	0	0	0
Total # pts expected for entire study:	5	Outpatient	8	0	0
		Scatter RN Hours	0	0	0
		Offsite Visits	0	0	0

RESEARCH BIONUTRITION	N	MULTICENTER STUDY	Y	
INFORMATICS CORE	Y	CLINICAL TRIAL	Y	Phase II-III
BIostatistician	N	CORE LAB	N	
ANCILLARIES ONLY	N			

INVESTIGATOR	DEPARTMENT	NON-HOST INSTITUTION: STATE, COUNTRY
SALAZAR, JUAN C MD	PEDIATRICS	
FEDER, HENRY MD	Medicine/Family Medicine	
KRAUSE, PETER MD	Pediatrics	

SUBPROJECT DESCRIPTION:

The primary objectives of this study are: to compare the combination of 2 NRTIs plus a protease inhibitor (PI) versus 2 Nucleoside Reverse Transcriptase (NRTIs) plus a non-nucleoside reverse transcriptase inhibitor (NNRTI) as initial therapy, followed by second-line therapy if failure occurs, in terms of their effects on a long-term virologic endpoint and to compare two different viral load criteria for switching from first-line to second-line therapy in HIV Antiretroviral Naïve Children > 30 Days and < 18 years of age.

SUBPROJECT PROGRESS:

PACTG 390 (Version 3.0) has had one transfer enrollment to the protocol over the reporting period. This brings total enrollment since the initiation of the study to two subjects. Both of these subjects are currently on study.

No changes will be made to the recruitment plans. This study has been closed to accrual.

There have been no unexpected safety concerns. The PACTG 390 team regularly reviews safety data from this study, and the most recent report for this time period was dated September 2006. Based on cumulative data from August 2002 through September 25, 2006, the protocol team has concluded that there are no safety concerns related to those regimens being administered in the study population that would warrant a change in or cancellation of the study at this time. Data will continue to be evaluated periodically and sites will be notified of important safety information every six months as long as there continue to be subjects on study follow-up. The next safety report came out shortly after this reporting period and was likewise free of any safety concerns.

SPID: 0501 **PROTOCOL:** 501 **TYPE:** RESEARCH

SHORT TITLE: PACTG 1020A

LONG TITLE: Pediatric Clinical Trials Group (PACTG) 1020A: A Phase I/II, Open-Label, Pharmacokinetic and Safety Study of a Novel Protease Inhibitor (BMS232632) in Combination Regimens in Antiretroviral Therapy (ART) -Naïve and Experienced HIV-Infected Infants, Ch

AIDS:	Y	TOTALS	A	B	D
		Inpatient	0	0	0
START DATE:	4/15/2003	Scatter Bed	0	0	0
Total # pts expected for entire study:	70	Outpatient	0	0	0
		Scatter RN Hours	0	0	0
		Offsite Visits	0	0	0

RESEARCH BIONUTRITION	N	MULTICENTER STUDY	Y	
INFORMATICS CORE	Y	CLINICAL TRIAL	Y	Phase I-II
BIostatistician	N	CORE LAB	N	
ANCILLARIES ONLY	N			

INVESTIGATOR	DEPARTMENT	NON-HOST INSTITUTION: STATE, COUNTRY
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SALAZAR, JUAN C MD	PEDIATRICS	
FEDER, HENRY MD	Medicine/Family Medicine	
KRAUSE, PETER MD	Pediatrics	

SUBPROJECT DESCRIPTION:

The primary objectives of this study are: to determine the pharmacokinetic profile and dosing schedule of the capsule formulation for BMS-232632 in combination with two Nucleoside Reverse Transcriptase Inhibitors (NRTIs) in HIV-infected children and adolescents; to determine the pharmacokinetic profile and dosing schedule for the powder formulation of BMS-232632 in combination with two NRTIs in Human Immunodeficiency Virus (HIV)-infected infants and young children; and to determine the safety and tolerability of BMS-232632 in HIV-infected infants, children and adolescents.

SUBPROJECT PROGRESS:

PACTG 1020A (Version 5.0) has had no new enrollments over the GCRC report period. Since the initiation of the study no subjects have been enrolled.

Due to funding changes throughout the PACTG/IMPAACT Network, we will no longer be able to offer this protocol.

SPID: 0502 **PROTOCOL:** 502 **TYPE:** RESEARCH

SHORT TITLE: PACTG 1021

LONG TITLE: Pediatrics Clinical Trials Group(PACTG) 1021: An Open-Label Study to Evaluate the Safety, Tolerance, Anti-Viral-Activity and Pharmacokinetics of Emtricitabine in Combination with Efavirenz and Didanosine in a Once Daily Regimen in HIV Infected Antir

AIDS:	Y	TOTALS	A	B	D
		Inpatient	0	0	0
START DATE:	7/1/2002	Scatter Bed	0	0	0
Total # pts expected for entire study:	40	Outpatient	0	0	0
		Scatter RN Hours	0	0	0
		Offsite Visits	0	0	0

RESEARCH BIONUTRITION	N	MULTICENTER STUDY	Y	
INFORMATICS CORE	Y	CLINICAL TRIAL	Y	Phase I-II
BIostatistician	N	CORE LAB	N	
ANCILLARIES ONLY	N			

INVESTIGATOR	DEPARTMENT	NON-HOST INSTITUTION: STATE, COUNTRY
SALAZAR, JUAN C MD	PEDIATRICS	
FEDER, HENRY MD	Medicine/Family Medicine	
KRAUSE, PETER MD	Pediatrics	

SUBPROJECT DESCRIPTION:

The primary objectives of this study are: to determine the long-term safety and tolerance of a regimen of Emtricitabine (FTC) + Efavirenz (EFV) + Videx (ddI) administered once daily in Human Immunodeficiency Virus (HIV)-infected pediatric subjects who are naive, or have very limited exposure, to antiretroviral therapy; and to determine the antiviral activity of a regimen of FRC + EFV + ddI administered once daily in treatment of naive, or very limited antiretroviral exposed, pediatric subjects.

SUBPROJECT PROGRESS:

ACTG 1021 (Version 2.0) has had no new enrollments over the study report period. There have been no enrollments to this protocol since the initiation of the study.

Due to funding changes throughout the PACTG/IMPAACT Network, we will no longer be able to offer this protocol.

SPID: 0505 **PROTOCOL:** 505 **TYPE:** RESEARCH

SHORT TITLE: Acute Intermittent Porphozym
LONG TITLE: A Multi-Center, Double-Blind, Randomized, Placebo-Controlled, Parallel Group Trial, Investigating the Efficacy and Safety of Porphozym (Recombinant Human Porphobilinogen Deaminase) in the Treatment of Acute Attacks in Acute Intermittent Porphozym (AI)

AIDS:	N	TOTALS	A	B	D
			Inpatient	0	0
START DATE:	5/21/2003	Scatter Bed	0	0	0
Total # pts expected for entire study:	8	Outpatient	0	0	0
		Scatter RN Hours	0	0	0
		Offsite Visits	0	0	0

RESEARCH BIONUTRITION	N	MULTICENTER STUDY	Y	
INFORMATICS CORE	N	CLINICAL TRIAL	Y	Phase II-III
BIostatistician	Y	CORE LAB	N	
ANCILLARIES ONLY	N			

INVESTIGATOR	DEPARTMENT	NON-HOST INSTITUTION: STATE, COUNTRY
BONKOVSKY, HERBERT L MD	MEDICINE/GASTROENTEROL OGY	

SUBPROJECT DESCRIPTION:

Acute Intermittent Porphozym (AIP) is caused by an inherited defect of the enzyme porphobilinogen deaminase (PBGD), the third enzyme in the biosynthetic pathway leading to heme. The new treatment, which has been made in a biological laboratory by modern methods of molecular biology, is a preparation of this enzyme, rhPBGD, Porphozym™. The purpose of the trial is to compare the efficacy and safety of Porphozym™ with that of placebo as a treatment of AIP in subjects with acute attacks. The placebo is an inactive material identical in appearance to the drug undergoing testing. The Danish/Swedish company, HemeBiotech A/S, will supply both Porphozym™ and placebo. After coming to the hospital with an acute attack, and signing the study consent form, you will be given treatment with either Porphozym™ or placebo. You will be assigned to a treatment based on a pre-determined order decided at random (like flipping a coin). Therefore you will have a 50% chance of receiving the new treatment. Neither your doctor nor you will know which treatment you will receive. Treatment will be given into a blood vessel (a vein) over a period of 48 hours. You will be followed until you are discharged from the hospital. 14 days and 28 days after end of treatment you will come to the outpatient clinic for a follow-up visit. If you do not experience a new attack before the last of these visits, you will be followed until your next attack or for 6 months, whichever comes first.

SUBPROJECT PROGRESS:

2 subjects entered at University of Connecticut Health Center (UCHC) site during report period and since initiation of study. Study is now closed to enrollment 33 subjects internationally entered in study 2 subjects total entered at UCHC Initial data analysis by Zymenex concluded that study drug was well-tolerated and led to rapid and sustained decreases in serum levels of porphobilinogen but was not superior to placebo for treatment of acute attacks of AIP. IV administration of the recombinant enzyme is not being investigated further, but studies continue to see whether the enzyme can be administered in such a way that more enzyme gets into hepatocytes, where it may have greater benefit. The results have been presented at the biennial international meeting on porphyrins and porphyrias, Rotterdam, Netherlands, April, 2007, and a full paper is in preparation.

SPID: 0506	PROTOCOL: 506	TYPE: RESEARCH
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SHORT TITLE: NSABP B-35

LONG TITLE: NSABP B-35: A Clinical Trial Comparing Anastrozole with Tamoxifen in Postmenopausal Patients with Ductal Carcinoma in situ (DCIS) Undergoing Lumpectomy with Radiation Therapy

AIDS:	N	TOTALS	A	B	D
		Inpatient	0	0	0
START DATE:	1/30/2003	Scatter Bed	0	0	0
Total # pts expected for entire study:	5	Outpatient	0	7	0
		Scatter RN Hours	0	0	0
		Offsite Visits	0	5	0

RESEARCH BIONUTRITION	N	MULTICENTER STUDY	Y	
INFORMATICS CORE	Y	CLINICAL TRIAL	Y	Phase III
BIostatistician	N	CORE LAB	N	
ANCILLARIES ONLY	N			

INVESTIGATOR	DEPARTMENT	NON-HOST INSTITUTION: STATE, COUNTRY
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KURTZMAN, SCOTT MD	Surgery	
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SUBPROJECT DESCRIPTION:

This Phase III randomized, double-blind study will evaluate the effectiveness of anastrozole compared to tamoxifen in preventing the subsequent occurrence of breast cancer (local, regional and distant recurrences, and contralateral breast cancer) in postmenopausal women with primary ductal carcinoma in situ (DCIS) treated with lumpectomy and breast radiation. In addition, this study will compare adjuvant anastrozole to tamoxifen in terms of time to invasive breast cancer, ipsilateral recurrence, contralateral breast cancer, other non-breast second primary cancers, osteoporotic fractures, disease-free survival, and overall survival. Also, B-35 will ascertain the effects of anastrozole on patients' symptoms and quality of life as compared to tamoxifen. Analysis will include an endpoint based on survival time adjusted for the quality of life experienced.

SUBPROJECT PROGRESS:

We have 6 patients currently on study. One patient discontinued study drug due to the mild expected side effects and w/resolution of her side effects. One patient experienced some mild side effects but is continuing with the study drug. The other 4 patients are receiving study drug and they are doing fine w/out side effects. There are no changes to the recruitment plan and no anticipated changes to be made to the protocol. There have been no unexpected safety concerns at this time. There have been no publications that have cited the GCRC.

SPID: 0511 **PROTOCOL:** 511 **TYPE:** RESEARCH

SHORT TITLE: Muscle Biopsy Frail vs Non-frail

LONG TITLE: Correlation of clinical outcome measures with high resolution muscle imaging in frail versus non-frail older individuals

AIDS:	N	TOTALS	A	B	D
		Inpatient	0	0	0
START DATE:	6/18/2003	Scatter Bed	0	0	0
Total # pts expected for entire study:	12	Outpatient	0	0	0
		Scatter RN Hours	0	0	0
		Offsite Visits	0	0	0

RESEARCH BIONUTRITION	N	MULTICENTER STUDY	N
INFORMATICS CORE	N	CLINICAL TRIAL	N
BIostatistician	Y	CORE LAB	N
ANCILLARIES ONLY	N		

INVESTIGATOR	DEPARTMENT	NON-HOST INSTITUTION: STATE, COUNTRY
KENNY, ANNE M MD	CENTER ON AGING	
KUCHEL, GEORGE A MD	CENTER ON AGING	
MOHLER, WILLIAM A PHD	GENETICS & DEV BIOLOGY	

SUBPROJECT DESCRIPTION:

Although frailty has been difficult to define, Fried and her colleagues have established criteria for frailty based on physical and psychological characteristics. These characteristics include unintentional weight loss (10 or more pounds per year), self-reported exhaustion, weakness as measured by grip strength, slow walking speed, and low physical activity (Fried et al., 2001). With a framework to examine frailty, we propose to explore more fully the pathophysiology of sarcopenia in frail and non-frail older individuals. In Frontera et al. 2000 and Balagopal et al. 1997, the authors hypothesized that sarcopenia largely results from the decreased ability for the replacement of dysfunctional contractile proteins within the myofilament lattice.

Exploiting the signal in Second Harmonic Image Microscopy (SHIM), which is derived from and sensitive to the local density and alignment of contractile proteins within muscle sarcomeres, this new mode of non-linear laser-scanning microscopy will allow quantitative analysis of both the histology and molecular structure of completely native, intact muscle tissue. Thus far, few studies to date have provided extensive and quantitative ultrastructural examination of muscle from very old individuals (Frontera et al. 2000). Fiatarone Singh and colleagues, reported data outlining aspects of muscle damage in frail elders using electron microscopy, which has limitations in comparison to SHIM.

SUBPROJECT PROGRESS:

The study to assess the differences in high resolution muscle imaging in frail and non-frail individuals and correlate the changes to clinical outcomes is ongoing. Preliminary data suggest that there may be measurable differences in muscle morphology in frail and non-frail adults or at least correlations with physical performance measures. We have worked in the last year to better objectively quantify the output from the high resolution imaging. We now believe we should compare samples from young and old adults. We have recruited 6 subjects (3 M, 3F) within the last year. The samples and data has been analyzed and we are again working out methodology issues with the second harmonic generation (SHG). We may need to recruit another 6 individuals once this methodology issue has been resolved. We have had no unexpected safety concerns. No further changes in protocol have been made. There have been no publications from the work but preliminary data was presented at the 2004 meeting (May) of the American Geriatrics Society in Washington, DC. We request further General Clinical Research Center (GCRC) support for the project while we continue to work through the laboratory methods and prepare to biopsy a final 6 subjects.

SPID: 0514	PROTOCOL: 514	TYPE: RESEARCH
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SHORT TITLE: Congestive Heart Failure

LONG TITLE: Anabolic and Catabolic State of Adults with Congestive Heart Failure (CHF) According to Level of Frailty

AIDS:	N	TOTALS	A	B	D
		Inpatient	0	0	0
START DATE:	6/19/2003	Scatter Bed	0	0	0
Total # pts expected for entire study:	90	Outpatient	0	0	0
		Scatter RN Hours	0	0	0
		Offsite Visits	0	0	0

RESEARCH BIONUTRITION	N	MULTICENTER STUDY	N
INFORMATICS CORE	N	CLINICAL TRIAL	N
BIostatistician	Y	CORE LAB	N
ANCILLARIES ONLY	N		

INVESTIGATOR	DEPARTMENT	NON-HOST INSTITUTION: STATE, COUNTRY
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BOXER, REBECCA MD	Medicine/Geriatrics	
HAGER, DAVID MD	Medicine/Cardio-Pulmonary	
KENNY, ANNE M MD	CENTER ON AGING	
MCELHANEY, JANET E MD	IMMUNOLOGY	

SUBPROJECT DESCRIPTION:

Background: Congestive heart failure (CHF) is common in those defined as frail. CHF may increase bone and muscle loss, due to either pathophysiology or treatment. In this study we set out to evaluate bone mineral density (BMD), and muscle mass in an older population with congestive heart failure compared with healthy aged matched controls.

Methods: Subjects were recruited from a university CHF clinic if ejection fraction (EF) was 40%. Healthy controls were recruited from the community. Participants were assessed for level of frailty with the 5-step frailty phenotype(1) including self reported weight loss, grip strength, energy level, walk time, and physical activity. Lean tissue masses, appendicular skeletal muscle mass/height² (ASM/Ht²) and bone mineral density were assessed by dual x-ray absorptiometry.

Results: There were 83 subjects; 60 with CHF (43M,17W), 23 (15M,8W) healthy age matched controls. The mean age of CHF men was 76.5+8.9 and women 77.7+12.2, control men 76.8+9.0, control women 78.1+10.6. NYHA classification was class I and II n=35; III and IV n= 25 and mean EF was 28.9+8.0. Frailty phenotype score for CHF was 28.3% (n=17) not frail, 45% (n=27) pre-frail, and 26.7% (n= 16) frail compared to controls 47.8% (n=11) not frail, 52.1% (n=15) pre-frail, and 0% frail. Sarcopenia was present in 12.5% women and 20.9% men with CHF, and 12.5% women and 26.7% men of controls. In separate regression models of femoral neck (fnBMD) and ASM/Ht², the variables of age and gender were significant (age p=0.007; p<0.00) and gender p=0.031, p<0.001) but the diagnosis of CHF was not. Regressions of fnBMD and ASM/Ht², controlling for age and sex, showed a significant relationship with frailty score (p= 0.02) and EF (p=0.03) for fnBMD. There was no relationship with frailty score or EF with ASM/Ht².

Conclusion: Older age, female gender, frailty score and ejection fraction all predict low fnBMD although the diagnosis of CHF does not. Age and female gender were also related to ASM/Ht², but frailty and EF were not. This work suggests that CHF severity may affect BMD and that individuals with CHF and frailty should be evaluated for osteoporosis. In this cohort of older adults, with CHF, sarcopenia was not related to CHF or frailty status.

SUBPROJECT PROGRESS:

The study recruited 83 individuals, 23 controls and 60 individuals with heart failure. No safety concerns were noted during the active phase of the trial. We are presently closed for recruitment but are actively analyzing data. We continue to use the services of the GCRC statisticians for the project. Manuscript preparations are ongoing. American Journal of Geriatric Cardiology Boxer R, Walsh S, Wang Z, Hager WD, Kenny AM Use of the Frailty Phenotype and 6-Minute Walk Test to Define a Syndrome of Pre-Frailty in Older Adults with Heart Failure. One is submitted to Journal of Cardiac Failure Boxer R, Walsh S, Wang Z, Hager WD, Kenny AM The Association of Vitamin D and Inflammation with the 6-Minute Walk and Frailty in Patients with Heart Failure Due to critiques from one of the papers, we will be extending the project to identify whether participants are alive and for those living, to reassess frailty

status. This project is just received Institutional Review Board (IRB) approval.

SPID: 0518	PROTOCOL: 518	TYPE: RESEARCH
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SHORT TITLE:	Skeletal Disorders
LONG TITLE:	Molecular Mechanisms for Skeletal Disorders

	AIDS:	N	TOTALS			
				A	B	D
			Inpatient	0	0	0
START DATE:	6/19/2003		Scatter Bed	0	0	0
Total # pts expected for entire study:		20	Outpatient	0	0	0
			Scatter RN Hours	0	0	0
			Offsite Visits	0	0	0

RESEARCH BIONUTRITION	N	MULTICENTER STUDY	N
INFORMATICS CORE	N	CLINICAL TRIAL	N
BIostatistician	N	CORE LAB	Y
ANCILLARIES ONLY	N		

INVESTIGATOR	DEPARTMENT	NON-HOST INSTITUTION: STATE, COUNTRY
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REICHENBERGER, ERNST PHD	Biostructure and Function	
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SUBPROJECT DESCRIPTION:

Cranio metaphyseal dysplasia (CMD) is a monogenic cranio tubular bone disorder, which is characterized by deposition of highly mineralized bone matrix in the cranium and face, whereas long bones exhibit flared metaphyses of decreased bone density. Diaphyses appear normal. Cherubism is a disorder of excessive bone degradation which affects only maxillary and mandibular bones. Excessive bone resorption occurs first in the cyst-like cavities of the mandible. Bone in the cavities is replaced by soft fibrous tissue. Jaw bones progressively resorb until in more severe cases only an outer shell of cortical bone remains. The soft stromal tissue proliferates and causes characteristic facial features. Isolated aplasia cutis congenita (ACC) manifests in congenital skin defects which are typically on the scalp, and the underlying cranial bone can be absent. Patients with trichodontoosseous syndrome (TDO) present with curled hair, enamel hypoplasia and hypocalcification of teeth, increased bone density of the skull and subtle undertubulation of long bones.

All of the above disorders occur as autosomal dominant (AD) traits, but also sporadically, and in the case of CMD, ACC, and cherubism also in an autosomal recessive (AR) fashion. Disease genes for the AD form of the disorders have been identified. However, there are a number of patients who did not have mutations in the known disease genes. The AD form of CMD is caused by mutations in ANK (Reichenberger et al., 2001), AD cherubism by mutations in SH3BP2 (Ueki et al., 2001), and TDO by a deletion in DLX3 (Price et al., 1998).

Our goal is to identify additional mutations in these genes which could help to explain the mode of action of the mutations during pathogenesis. We also attempt to identify and recruit families which do not map to the known loci and perform genome-wide screening, especially for cherubism and ACC.

SUBPROJECT PROGRESS:

Total number of patients enrolled: 370 Current Year Enrollment: 16 Changes in recruitment plans that might be needed: None Unexpected safety concerns and their resolution: None Interim data and outcomes: Research in the past year was directed on the analysis of mouse models for the human disorders Cherubism and Cranio metaphyseal Dysplasia. Recruitment of human subjects is still ongoing, especially for jCherubism where we will test human specimen for results which we gained from studies in an animal system. Deoxyribonucleic acid (DNA) samples from ACC patients will be subjected to genome-wide screening and linkage analysis. Recruitment efforts will be increasing in the future. Proposed changes made or anticipated in the protocol: None Publications (with mention of the GCRC): None

SPID: 0519 **PROTOCOL:** 519 **TYPE:** RESEARCH

SHORT TITLE: Enhanced and Attendance-Based Prize

LONG TITLE: Enhanced and Attendance-Based Prize Contingency Management for Drug Users in Community Settings

AIDS:	N	TOTALS	A	B	D
			Inpatient	0	0
START DATE:	8/21/2003	Scatter Bed	0	0	0
Total # pts expected for entire study:	450	Outpatient	0	0	0
		Scatter RN Hours	0	0	0
		Offsite Visits	1,652	0	0

RESEARCH BIONUTRITION	N	MULTICENTER STUDY	N
INFORMATICS CORE	N	CLINICAL TRIAL	N
BIostatistician	N	CORE LAB	N
ANCILLARIES ONLY	N		

INVESTIGATOR	DEPARTMENT	NON-HOST INSTITUTION: STATE, COUNTRY
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PETRY, NANCY M PHD	PSYCHIATRY	
ALESSI, SHELIA PHD	Psychiatry	

SUBPROJECT DESCRIPTION:

In our research evaluating contingency management (CM) that provides opportunities to win prizes, we have noted that the efficacy of CM may be dependent on the status of the individual as they initiate treatment. Patients who begin treatment with a cocaine-positive urinalysis result tend to drop out of treatment prematurely and to continue using while in treatment. CM interventions have been efficacious in reducing drug use in this subgroup, and the effects were magnitude dependent. However, we have thus far only tested up to a maximum of \$250 in prizes, and larger magnitudes may further improve outcomes. One purpose of this proposal is to examine the efficacy of an enhanced CM procedure, in which increased frequencies of prize winnings are provided during initial periods of abstinence. Cocaine-dependent patients beginning treatment with a cocaine-positive urine sample (N=120) will be randomly assigned to one of three conditions: (a) standard, non-CM treatment, (b) standard treatment plus CM with an expected probability of winning about \$250 in prizes, or (c) standard treatment plus CM with an expected probability of winning about \$560 in prizes.

We have also found that patients who present to treatment with cocaine-negative samples generally remit negative samples throughout their time in treatment, regardless of whether they received a non-CM or a CM treatment contingent upon abstinence. Thus, we will also conduct a parallel study that will assess whether simply reinforcing attendance at treatment enhances retention and improves long-term outcomes in this subgroup. Cocaine-dependent patients (N=330) initiating treatment with a cocaine-negative urine sample will be randomly assigned to one of three conditions: (a) standard treatment without CM or (b) standard treatment plus CM with an expected probability of winning about \$250 worth of prizes contingent upon cocaine abstinence, or (d) standard treatment plus CM with an expected probability of winning about \$250 worth of prizes contingent upon treatment attendance. Together, these studies will address the conditions under which lower and higher cost prize CM procedures may improve outcomes of cocaine-dependent patients

SUBPROJECT PROGRESS:

Total Enrollment: 374 Past Year Enrollment: 109 · No changes in recruitment plans are needed. · No unexpected safety concerns have occurred. · Interim data and outcomes are not available. · No changes were made to the protocol and none are anticipated. · No publications since previous annual report.

SPID: 0520 **PROTOCOL:** 520 **TYPE:** RESEARCH

SHORT TITLE: Contingency Management for Methadone Patients

LONG TITLE: Enhanced and Attendance-Based Prize Contingent Management (CM) in Community Settings

AIDS:	N	TOTALS	A	B	D
		Inpatient	0	0	0
START DATE:	8/21/2003	Scatter Bed	0	0	0
Total # pts expected for entire study:	120	Outpatient	0	0	0
		Scatter RN Hours	0	0	0
		Offsite Visits	95	0	0

RESEARCH BIONUTRITION	N	MULTICENTER STUDY	N
INFORMATICS CORE	N	CLINICAL TRIAL	N
BIostatistician	N	CORE LAB	N
ANCILLARIES ONLY	N		

INVESTIGATOR	DEPARTMENT	NON-HOST INSTITUTION: STATE, COUNTRY
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PETRY, NANCY M PHD	PSYCHIATRY	
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ALESSI, SHELIA PHD	Psychiatry	
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SUBPROJECT DESCRIPTION:

Voucher-incentive contingency management (CM) interventions are efficacious in enhancing retention in treatment and reducing cocaine use. However, voucher procedures have rarely been implemented or tested in community-based treatment programs, primarily due to cost. A lower-cost CM procedure, that provides opportunities to win prizes ranging in value from \$1 to \$100, shows efficacy in applied treatment settings. This study will compare directly the voucher and prize procedures. 120 methadone maintained patients meeting Diagnostic and Statistical Manual of Mental Disorders, 4th Edition (DSM-IV) criteria for cocaine dependence will be randomly assigned to one of three conditions: (a) standard treatment plus CM in which subjects can earn up to \$585 in vouchers; (b) standard treatment plus CM with an expected probability of winning \$300 worth of prizes; or (c) a control condition-- standard treatment without CM. In the two CM conditions, subjects will be reinforced for providing drug-free urine specimens. Drug use, severity of psychosocial problems, and Human Immunodeficiency Virus (HIV) risk behaviors will be measured pre-treatment, during a 3-month treatment period, and throughout a 6-month follow-up period. Additionally, we will evaluate the cost-effectiveness of the interventions by assessing subjects' receipt of psychosocial and medical services, as well as criminal justice system involvement. Both CM conditions are expected to improve outcomes relative to standard treatment, but whether the two CM conditions are equally efficacious is a question of interest.

SUBPROJECT PROGRESS:

Total Enrollment: 76 Past Year Enrollment: 0 · No changes in recruitment plans are needed. · No unexpected safety concerns have occurred. · Interim data and outcomes are not available. · No changes were made to the protocol and none are anticipated. · No publications since previous annual report.

SPID: 0523	PROTOCOL: 523	TYPE: RESEARCH
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SHORT TITLE:	Mif Genotyping
LONG TITLE:	Mif Genotyping and Osteoporosis

	AIDS:	N	TOTALS	A	B	D
			Inpatient	0	0	0
START DATE:		9/18/2003	Scatter Bed	0	0	0
Total # pts expected for entire study:		250	Outpatient	0	0	0
			Scatter RN Hours	0	0	0
			Offsite Visits	0	0	0

RESEARCH BIONUTRITION	N	MULTICENTER STUDY	N
INFORMATICS CORE	N	CLINICAL TRIAL	N
BIostatistician	Y	CORE LAB	Y
ANCILLARIES ONLY	N		

INVESTIGATOR	DEPARTMENT	NON-HOST INSTITUTION: STATE, COUNTRY
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KENNY, ANNE M MD	CENTER ON AGING	
JOSEPH, CHERIAN MD	Medicine/Geriatrics	

SUBPROJECT DESCRIPTION:

Fracture risk as measured by low Bone Mineral Density (BMD), is found to be genetically determined. Family history of hip fracture predicts osteoporotic fracture independently from bone mass. It is unclear whether many genes, each with small effects or small number of genes with somewhat larger effects are responsible for the genetic contribution determining BMD. Inheritance of BMD at the hip has been estimated to be between 70-85%. Nevertheless, many factors play a role in predicting the development of a fracture including bone mass, as well as the quality, and geometry of the bone architecture.

Potential candidate genes, which may contribute to the development of osteoporosis include genes coding for bone matrix proteins, adhesion molecules and ligands, hormones and their receptors, as well as enzymatic pathways (e.g. Aromatase, Matrix Metalloproteinases (MMPs)). Although many genetic studies have already been done, further work needs to be done looking for a candidate gene with major effect on molecular or cellular mechanism underlying osteoporosis.

Research Hypothesis: We propose that individuals with a higher mean CATT (cytosine, adenine, thymine, thymine) repeats in the Mif gene will have lower bone mineral density than individuals with lower mean CATT repeats.

SUBPROJECT PROGRESS:

The study is now closed to recruitment. There were no changes to recruitment plans. There were no reported adverse effects or safety concerns. Analysis and work to obtain access to a national database to obtain adequate sample size is ongoing. Preliminary analysis follows: The distribution of Mif genotype are as follows: 5,5 genotype were 5/86 (5.81%); 5,non 5 genotype present in 26 (30.2%); and non 5, non 5 present in 55 (63.9%) participants. The mean femoral neck BMD for those with any 5 allele (low expressing genotype) was 0.89 ± SD 0.13 and for group with no 5 allele (high expressing genotype) was 0.84 ± SD 0.13 difference of 0.06 in bone density. (p= 0.063). There was no significant contribution of CATT genotype to femoral neck bone density (F 1.64, P=0.204.) when adjusted for age, gender, and Body Mass Index. Conclusions: In this preliminary pilot study, no difference was seen in femoral neck bone density between individuals with low- and high-expressing Mif alleles once potentially confounding variables were controlled. A larger sample cohort will be required to adequately address the study hypothesis. The data was presented at the 2004 annual meeting of the Society for Bone and Mineral Research. No publications from the data are available to date. We are presently attempting to expand the work with collaborators in Europe to assess similar issues in a large population based study. If this can be accomplished, manuscript preparation will begin. Continuing GCRC resources are required for continued data analysis and manuscript preparation.

SPID: 0524	PROTOCOL: 524	TYPE: RESEARCH
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SHORT TITLE: Influenza Risk

LONG TITLE: T-Cell Responses Predict Influenza Risk in Older Adults and Cytokines in Innate Immunity: Effect on Cytotoxic T Lymphocytes (CTL)

AIDS:	N	TOTALS	A	B	D
		Inpatient	0	0	0
START DATE:	9/18/2003	Scatter Bed	0	0	0
Total # pts expected for entire study:	160	Outpatient	562	0	0
		Scatter RN Hours	0	0	0
		Offsite Visits	0	0	0

RESEARCH BIONUTRITION	N	MULTICENTER STUDY	N
INFORMATICS CORE	Y	CLINICAL TRIAL	N
BIostatistician	N	CORE LAB	N
ANCILLARIES ONLY	N		

INVESTIGATOR	DEPARTMENT	NON-HOST INSTITUTION: STATE, COUNTRY
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MCELHANEY, JANET E MD	IMMUNOLOGY	
HAGER, DAVID MD	Medicine/Cardio-Pulmonary	

SUBPROJECT DESCRIPTION:

Aging causes a decline in cell-mediated immunity (CMI) and is associated with a tremendous increase in the late-life morbidity from influenza infections. Vaccination can prevent influenza illness but current vaccines are only 50-60% effective in the over 65 population (versus 90% in younger adults). Even with this limited efficacy, influenza vaccination is a cost-saving intervention due to the reduction in hospitalization for acute respiratory illness and congestive heart failure (CHF). This proposal outlines a strategy to advance the basic science of influenza learned from studies in the aged mouse model, to application in a very high-risk population of older adults with CHF. Identifying age and CHF-related changes in the innate and adaptive immune responses to influenza and influenza vaccination, is imperative to the development of new vaccines or adjuvant therapies for improved prophylaxis in older people.

The long-range goal of this project is to use translational methodology to determine the mechanism by which age and disease-related factors increase the risk of influenza and diminish vaccine efficacy. The objective of this application is to characterize protective immunologic responses, compare the level of immunity in different risk groups, and finally define the level of laboratory measures that predict outcomes of illness in older people. In the process, clinical and laboratory measures will be developed as individual and population indicators of how risk for influenza illness is altered by vaccination and including clinical trials of new vaccines.

The central hypothesis of the application is that the level of granzyme B (Grz B) in influenza-specific cytotoxic T lymphocytes (CTL) predicts risk for influenza illness. Grz B levels decrease with advancing age and functional decline due to a dysregulation of T-cell function that is not reversed by vaccination with killed influenza virus. The rationale for the proposal is that older adults with CHF have a very high-risk for serious complications of influenza and suggests that the senescent immune response to influenza is further compromised in the presence of CHF. Influenza attack rates are higher and vaccine efficacy is lower in this population. CHF in older adults thus provides a model for studying immunologic responsiveness that can be linked to clinical outcomes. Very high-risk groups of older adults who continue to suffer disabling consequences of influenza due to poor responses to current killed-virus vaccines can then be targeted for new prophylaxis strategies. Recent studies have highlighted the role of Toll-like receptors (TLR) in the transition from innate to adaptive immune responses. TLR recognize pathogen-associated molecular patterns (PAMP) and stimulate cytokine production by a number of cells including Th type 1 (Th1), creating the necessary microenvironment to stimulate effector mechanisms such as CTL. In viral infections, it is critical that the transition from the innate to adaptive immune response activates cytotoxic T-lymphocytes (CTL) to kill virus-infected host cells. The methodology derived from this work will be critical for screening new vaccines for immunologic responsiveness prior to expensive, large clinical trials. In the interim, it will be possible to combine vaccination with the use of antiviral drugs in those very high-risk groups with poor responses to current vaccines.

SUBPROJECT PROGRESS:

Studies and Results A significant milestone has been achieved in this project with the definition of a threshold level of GrzB as a correlate of protection against influenza illness in vaccinated older adults. The combined results of two studies have shown that the ex

vivo GrzB assay distinguishes different subsets of vaccinated older adults including those who develop influenza, those who do not, and those who have an enhanced response to vaccination due to concurrent or recent influenza infection (McElhane et al, J Immunol 2006; McElhane et, submitted). From this analysis, a threshold level of GrzB is defined at 200 U/mg protein as a correlate of protection in older adults. Combined results from these two studies also show that influenza attack rates are similar in older adults without CHF compared to those with CHF suggesting that influenza vaccination has similar efficacy for preventing influenza in different risk groups of older adults. Clinical variables including performance on the 6 minute walk test (6-MWT) and the use of statin drugs are determinants of interferon (IFN)-ratios and Grz B levels prior to vaccination but as a covariate of risk for influenza illness in vaccinated older adults remains to be determined. In contrast, these two studies have now shown that in the older adult population, antibody responses to or antibody titers following influenza vaccination do not distinguish those vaccinated older adults who will develop influenza illness from those who do not. (McElhane et al, J Immunol 2006; McElhane et al, submitted) Fluorescence Activated Cell Sorting (FACS) analysis shows that the previously documented increase in CD28- CTL (lack cytolytic activity) in older vs young adults; the proportion of CD28- is negatively correlated with the proportion of virus-specific memory CTL (GrzB+CD62LhighCD8+) in older adults. The strength of this correlation increases following vaccination suggesting that the proportion of CD28- CTL is a determinant of the CTL response to influenza vaccination. (Xie D, et al, submitted) Other studies suggest that this subset is both CD4+ and CD8+ in older adults and this CD4+CD8+ subset may become the reservoir for influenza-specific memory CTL with aging. c. Significance This research program is completely aligned with the NIH Roadmap promoting translational research and delivers a public health message. All older persons benefit from influenza vaccination; it reduces the risk of influenza illness in persons with high-risk conditions to that of healthier older adults. Also, older people should know that even if they get the flu, they are much less likely to become seriously ill, and in the next year, can anticipate even better protection through vaccination. Our research suggests that a targeted approach to stimulating CTL-mediated immunity would significantly improve vaccine efficacy over current split-virus vaccines in older adults. Further, the GrzB assay could be used as a surrogate of vaccine efficacy to screen these redesigned influenza vaccines and fast track development through the pre-clinical and early phases of clinical trials. Most importantly, we have shown that antibody responses are not effective as a sole predictor of vaccine efficacy in this population. A new correlate of vaccine protection based on cell-mediated immunity can be used to fast track the development of both seasonal and pandemic vaccines for older adults. d. Plans The experimental plan will continue with a targeted enrollment of 150 older adults with or without CHF or ACS (150 subjects) and 20 young adults on annual basis to study the immune response to influenza vaccination. Surveillance during the influenza season documents influenza cases confirmed by virus culture or PCR, or seroconversion. The following is a summary of the current experimental plan: In Aim 1, a panel of cytokines and chemokines (multiplex assays) in influenza-stimulated PBMC supernatants and GrzB at 0, 4, and 10 weeks post-vaccination. Cytokines/chemokines that promote a Th1 vs. Th2 response to influenza will be identified. Subjects are characterized according to underlying CHF, ACS, or not, and clinical factors shown to affect the immune response including medications (mainly statin lipid-lowering drugs), and performance on a 6-minute Walk Test (6-MWT). In Aim 2, FACS analysis evaluates the effect of CD28- CTL on response to influenza within the central memory subset of virus-specific CTL (GrzB+CD62LhighCD8+) pre- and 4-weeks post-vaccination, and the effect of inflammatory cytokines including macrophage migration inhibitory factor (MIF) on the CTL response to influenza vaccination. Interactions between the different cytokines/chemokines are evaluated in Aim 1 and then tested for their effects ex vivo or in vitro. RNA extracted from influenza-stimulated PBMC is isolated at 10-weeks post-vaccination for microarray analysis. In Aim 3, unstimulated Peripheral Blood Mononuclear Cell (PBMC) will be frozen at 20-weeks post-vaccination for shipment to our collaborator, Dr. Tania Watts (University of Toronto). Our methods for freezing PBMC have been shown to be reliable for testing paired samples (i.e., CTL responses with vs. without costimulation). These studies will determine the potential for enhanced costimulation to improve vaccine efficacy in older adults.

SPID: 0526 **PROTOCOL:** 526 **TYPE:** RESEARCH

SHORT TITLE: Oral Candida

LONG TITLE: Oral Epithelial Cells, Candida and Polymorphonuclear Leukocyte (PMN) Activation

AIDS:	N	TOTALS	A	B	D
		Inpatient	0	0	0
START DATE:	9/25/2003	Scatter Bed	0	0	0
Total # pts expected for entire study:	20	Outpatient	13	0	0
		Scatter RN Hours	0	0	0
		Offsite Visits	0	0	0

RESEARCH BIONUTRITION	N	MULTICENTER STUDY	N
INFORMATICS CORE	Y	CLINICAL TRIAL	N
BIostatistician	N	CORE LAB	N
ANCILLARIES ONLY	N		

INVESTIGATOR	DEPARTMENT	NON-HOST INSTITUTION: STATE, COUNTRY
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DONGARI-BAGTZOGLU, ANNA I DDS, PHD	PERIODONTOLOGY	
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SUBPROJECT DESCRIPTION:

Oral candidiasis is perhaps the most frequent opportunistic infection associated with an immunocompromised host. The most important immune cell type in the defense against Candida is the neutrophil (PMN). Although these cells are considered important in the resistance to and eradication of fungi, expression of these functions requires activation by soluble proteins known as cytokines. In the immunocompromised host these molecules are more likely to be derived from cells of non-immune origin, such as epithelial cells. The purpose of this study is to test the activation of neutrophil anti-fungal functions in response to cytokines secreted by oral epithelial cells.

SUBPROJECT PROGRESS:

Since the initiation of the study we enrolled 18 subjects. During the last report period, we recruited 5 subjects. Recruited human subjects at the GCRC provided the neutrophils used in in vitro experiments. We expect recruitment rates to remain the same during the next year of funding by the National Institutes of Health (NIH)(RO1). There are no unexpected concerns or changes in the protocol. Data on the human subjects recruited over the past year will be presented at the 2nd International Conference on the Crossroads between Innate and Adaptive Immunity, in June 2007. These studies demonstrated that oral epithelial cells can play an immunoregulatory role in oral fungal infections, using a three dimensional in vitro model of the human oral mucosa. (REGULATION OF NEUTROPHIL ANTI-FUNGAL ACTIVITIES IN A THREE-DIMENSIONAL MODEL OF ORAL CANDIDIASIS. A. DONGARI-BAGTZOGLU, H. KASHLEVA)

SPID: 0528	PROTOCOL: 528	TYPE: RESEARCH
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SHORT TITLE: Fabry Registry

LONG TITLE: Fabry Registry

AIDS:	N	TOTALS	A	B	D
		Inpatient	0	0	0
START DATE:	11/20/2003	Scatter Bed	0	0	0
Total # pts expected for entire study:	40	Outpatient	34	0	0
		Scatter RN Hours	0	0	0
		Offsite Visits	0	0	0

RESEARCH BIONUTRITION	N	MULTICENTER STUDY	Y	
INFORMATICS CORE	N	CLINICAL TRIAL	Y	Phase IV
BIostatistician	N	CORE LAB	Y	
ANCILLARIES ONLY	N			

INVESTIGATOR	DEPARTMENT	NON-HOST INSTITUTION: STATE, COUNTRY
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GREENSTEIN, ROBERT MD	Pediatrics/Genetics	
ADAMS, NANCY MD	Medicine/Nephrology	
BONA, ROBERT MD	Medicine/Hem-Onc	
COBB, RICHARD MD	Diagnostic Imaging	
LEWIS, COURTLAND MD	Orthopedics	
RAISZ, LAWRENCE G MD	Medicine/Endocrinology	
SILVERMAN, DAVID I MD	Medicine	
WHITAKER, CHARLES MD	Medicine/Neurology	

SUBPROJECT DESCRIPTION:

The Fabry Registry is an ongoing, observational database that tracks the natural history and outcomes of patients with Fabry disease. Participation is open to all physicians managing patients with Fabry disease. Physicians are encouraged to collaborate, share observations, and generate hypotheses for evaluation, as well as assist in the collection of clinical data in an effort to guide and assess future therapeutic interventions.

SUBPROJECT PROGRESS:

Since initiation of this study, there have been 45 Fabry subjects enrolled, and of these, 34 are active in the Registry. The project is discontinued as of 12/31/06, with a no cost extension through 6/30/07. The PI will not continue after 6/30/07. There were no changes to the protocol. There were no unexpected safety concerns, interim data or outcomes to report.

SPID: 0529 **PROTOCOL:** 529 **TYPE:** RESEARCH

SHORT TITLE: Gaucher Registry

LONG TITLE: Gaucher Registry

AIDS:	N	TOTALS	A	B	D
		Inpatient	0	0	0
START DATE:	11/20/2003	Scatter Bed	0	0	0
Total # pts expected for entire study:	40	Outpatient	6	0	0
		Scatter RN Hours	0	0	0
		Offsite Visits	0	0	0

RESEARCH BIONUTRITION	N	MULTICENTER STUDY	Y	
INFORMATICS CORE	Y	CLINICAL TRIAL	Y	Phase IV
BIostatistician	N	CORE LAB	Y	
ANCILLARIES ONLY	N			

INVESTIGATOR	DEPARTMENT	NON-HOST INSTITUTION: STATE, COUNTRY
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GREENSTEIN, ROBERT MD	Pediatrics/Genetics	
ADAMS, NANCY MD	Medicine/Nephrology	
BONA, ROBERT MD	Medicine/Hem-Onc	
COBB, RICHARD MD	Diagnostic Imaging	
LEWIS, COURTLAND MD	Orthopedics	
RAISZ, LAWRENCE G MD	Medicine/Endocrinology	
SILVERMAN, DAVID I MD	Medicine	
WHITAKER, CHARLES MD	Medicine/Neurology	

SUBPROJECT DESCRIPTION:

The Gaucher Registry is an ongoing, post-marketing, observational database that tracks outcomes of routine clinical practice for patients with Gaucher disease. Not all patients in the Registry are on Enzyme Replacement Therapy (ERT). All physicians participating in the Registry are considered members of the International Collaborative Gaucher Group (ICGG). Data collected from ICGG physicians will represent Gaucher disease practice patterns under common clinical conditions. Thus, the data collected by this international, collaborative Registry will provide information to better characterize the natural history and progression of Gaucher disease, as well as the clinical responses of patients whose physicians have prescribed ERT.

SUBPROJECT PROGRESS:

Since our last report on this project, there have been no new subjects enrolled. We continue to collect Registry data on 19 subjects. There are no changes in recruitment plans. There were no unexpected safety concerns and no major adverse events. There is no interim data to report nor outcomes to report. The participation of the PI will end 6/30/07 and the funding is completed as of 12/31/06 with a no cost extension through 6/30/07.

SPID: 0530	PROTOCOL: 530	TYPE: RESEARCH
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SHORT TITLE: Gleevec Resistance

LONG TITLE: Study of the Mechanisms of Gleevec Resistance in Chronic Myelogenous Leukemia (CML) CML Patients

	AIDS:	N	TOTALS	A	B	D
			Inpatient	0	0	0
START DATE:		10/16/2003	Scatter Bed	0	0	0
Total # pts expected for entire study:		44	Outpatient	0	0	0
			Scatter RN Hours	0	0	0
			Offsite Visits	0	0	0

RESEARCH BIONUTRITION	N	MULTICENTER STUDY	N
INFORMATICS CORE	Y	CLINICAL TRIAL	N
BIostatistician	N	CORE LAB	Y
ANCILLARIES ONLY	N		

INVESTIGATOR	DEPARTMENT	NON-HOST INSTITUTION: STATE, COUNTRY
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FANG, MIN MD, PHD	Genetics & Dev. Biology	
LI, ZIHAI MD, PHD	Ctr for Immunotherapy	

SUBPROJECT DESCRIPTION:

Cutaneous basal cell carcinoma (BCC) and squamous cell carcinoma (SCC) are the two most common cancers in the U.S.. While they both arise from the epidermis, these cancers differ dramatically in biological behavior and their underlying gene expression patterns have not been compared. We thus examined Messenger Ribonucleic Acid (mRNA) transcript levels in these malignancies as well as in psoriasis, a benign epidermal hyperplasia. Transcript expression patterns distinguish these disorders and identify differentially expressed genes. Among these is Egr-1, whose epidermal expression is consistently decreased in BCC and SCC but is elevated in psoriasis. Our preliminary data indicated that Egr-1 inhibits accelerated growth of benign and malignant epidermal cells in association with suppression of Cdc25A expression. We would like to confirm this finding and further investigate whether the phosphorylation status and kinase activity of Cdk2, a downstream target of Cdc25A, are affected. We hypothesize that gene expression profiling can differentiate epidermal hyperproliferative diseases and identify a role for Egr-1 in preventing uncontrolled epidermal growth.

SUBPROJECT PROGRESS:

Number of subjects enrolled during the report period and since initiation of the study: 15 Current Year Enrollment: 3 ?Any changes in recruitment plans that might be needed No ?Unexpected safety concerns and their resolution No ? Interim findings: Sequence analysis has shown mutations in samples from patients with Gleevec resistance. The hypothesis remains sound and continuation of the investigation is justified by the data obtained so far. ?Any proposed changes made or anticipated in the protocol No ?Publications N/A

SPID:	0531	PROTOCOL:	531	TYPE:	RESEARCH	
SHORT TITLE:	Sertraline Pharmacotherapy					
LONG TITLE:	Sertraline Pharmacotherapy for Alcoholism Subtypes					
AIDS:	N	TOTALS		A	B	D
		Inpatient		0	0	0
START DATE:	10/29/2003	Scatter Bed		0	0	0
Total # pts expected for entire study:	160	Outpatient		191	0	0
		Scatter RN Hours		0	0	0
		Offsite Visits		0	0	0
RESEARCH BIONUTRITION	N	MULTICENTER STUDY		Y		
INFORMATICS CORE	Y	CLINICAL TRIAL		Y	Phase IV	
BIostatistician	N	CORE LAB		Y		
ANCILLARIES ONLY	N					

INVESTIGATOR	DEPARTMENT	NON-HOST INSTITUTION: STATE, COUNTRY
KRANZLER, HENRY R MD	PSYCHIATRY	
COVAULT, JONATHAN MD, PHD	Psychiatry	
DEMARTINIS, NICHOLAS MD	Psychiatry	
HERNANDEZ-AVILA, CARLOS MD	Psychiatry	
NELLISSERY, MAGGIE MD	Psychiatry	
ONCKEN, CHERYL MD	Medicine	
TENNEN, HOWARD PHD	Community Medicine	

SUBPROJECT DESCRIPTION:

During the past decade, the pharmacotherapy of alcoholism has received increasing attention both from National Institute on Alcohol Abuse and Alcoholism (NIAAA) and the pharmaceutical industry. However, despite the Federal Drug Administration (FDA) approval of naltrexone for relapse prevention, medications are still not widely used to treat the disorder. This contrasts sharply with the treatment of nicotine dependence, for example, as well as other psychiatric disorders. In an effort to broaden the options for pharmacotherapy of alcoholism, this proposal will examine the effects of sertraline, a selective serotonin reuptake inhibitor (SSRI), for the treatment of alcohol dependence. The study is based on evidence that, although SSRI therapy is not appropriate for all alcoholics (Kranzler et al. 1996a, Pettinati et al. 2000), there exists a substantial subgroup with the disorder (i.e., Type A or later-onset alcoholics) for whom SSRI's appear to exert a clinically important effect. Since sertraline is well tolerated and among the most widely prescribed psychotropic medications in the world, a prospective demonstration of its efficacy could have a broad influence on the treatment of alcohol dependence. Consequently, this study will examine the safety and efficacy of sertraline, the mechanism and duration of those effects and the best method for subtyping alcoholics to identify individuals for whom the medication is most likely to produce a clinically important reduction in drinking behavior.

SUBPROJECT PROGRESS:

A total of 28 subjects were enrolled during the report period (a total of 93 since initiation of the study). As of 3/31/07, a total of 84 subjects had been randomized to receive treatment with either sertraline or placebo. There are no changes in recruitment plans. Institutional Review Board (IRB) approval was obtained during annual continuation review in April 2006 for using broadcast emails to recruit for the study and to post flyers in various community settings, health fairs/events, and local colleges). There have been no unexpected safety concerns associated with this study. Interim outcomes data are not available at this time. This study uses interactive voice response technology (IVR) for daily data collection, with support from the General Clinical Research Center (GCRC). The overall completion rate for IVR calls exceeds 87% among subjects while in treatment and 61% for all subject days. There have been no recent publications associated with this study since data collection is ongoing. Changes made in the protocol during the report period were: 1) a Waiver of Consent for phone screening was obtained (as per IRB guidance on this issue), and 2) modifications were made to the telephone script (to allow for referral of phone excludes to other active studies) and telephone screen (removed a Protected Health Information (PHI) question unnecessary for preliminary eligibility screening).

SPID: 0534 **PROTOCOL:** 534 **TYPE:** RESEARCH

SHORT TITLE: gp96 and Dendritic Cells
LONG TITLE: Receptor for gp96 on Macrophages and Dendritic Cells

AIDS:	N	TOTALS	A	B	D
			Inpatient	0	0
START DATE:	11/7/2003	Scatter Bed	0	0	0
Total # pts expected for entire study:	6	Outpatient	0	0	0
		Scatter RN Hours	0	0	0
		Offsite Visits	0	0	0

RESEARCH BIONUTRITION	N	MULTICENTER STUDY	N
INFORMATICS CORE	Y	CLINICAL TRIAL	N
BIostatistician	N	CORE LAB	N
ANCILLARIES ONLY	N		

INVESTIGATOR	DEPARTMENT	NON-HOST INSTITUTION: STATE, COUNTRY
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SRIVASTAVA, PRAMOD K PHD	IMMUNOLOGY	
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SUBPROJECT DESCRIPTION:

The known roles of Heat Shock Proteins (HSPs) can be grouped into two broad categories: chaperones of antigenic peptides and stimulators of innate immunity. Both of these functions depend on HSP interaction with receptors on Antigen Presenting Cells (APC). It is not clear which HSP receptors are involved with the innate versus the adaptive component of HSP-elicited immunity. Receptors that signal but do not endocytose (i.e. are logical candidates for innate immunity) include TLR2, TLR4, CD40 and CD36. Receptors that endocytose (i.e. are logical candidates for adaptive immunity) include LOX-1 and CD91. CD91 was the first HSP receptor to be identified and its role in HSP-elicited immunity is presently the most thoroughly understood.

This study aims to further assess and identify HSP receptors on antigen-presenting murine (mouse) and human Dendritic Cells (DC). This will be accomplished via two mostly independent experimental aims. Aim 1a will assess the role of LOX-1 and other HSP receptors relative to CD91 in the cross-presentation of HSP-chaperoned peptides. Aim 1b will generate monoclonal antibodies to human HSP receptors to identify new HSP receptors and better characterize already-known receptors. Aim 1a will utilize established mouse and human re-presentation systems to evaluate the ability of receptor ligands to inhibit the re-presentation of HSP-chaperoned antigens. Inhibition of the re-presentation system would support the involvement of that particular receptor in the cross-presentation of HSP-chaperoned antigens. The role of CD40 will be further investigated by determining the ability of a DM40^{-/-} mouse to generate an antigen-specific CD8⁺ T-cell response. Aim 1b will utilize blood monocyte-derived immature human DCs to generate monoclonal antibodies in mice and rats. Following immunization and sera collection, the spleen cells will be fused with mouse or rat myeloma cells to create hybridomas. The resulting monoclonal anti-human DC antibodies will be tested for their ability to inhibit re-presentation of HSP-chaperoned antigen. Hybridomas that produce anti-HSP receptor antibodies will be further characterized.

The results of this study have enormous potential for affecting human health. Numerous studies have shown that HSP-peptide complexes isolated from cancer or virus-infected cells can be used as vaccines against the cancer or virus concerned without eliciting detectable autoimmunity.

SUBPROJECT PROGRESS:

This project is ongoing. Subjects will be contacted for enrollment and blood draws in the GCRC. -Number of subjects enrolling during the report period and since initiation of the study: None enrolled during the report period. Since the initiation of the study, 7 recruited, of which 3 met the inclusion criteria. -Any changes in recruitment plans that might be needed: None. -Unexpected safety concerns and their resolution: None. -Interim data and outcomes if appropriate: N/A. -Any proposed changes made or anticipated in the protocol: None. -Publications, indicating whether the GCRC was cited: The study is still in progress.

SPID: 0535 **PROTOCOL:** 535 **TYPE:** RESEARCH

SHORT TITLE: The Effects of Oral Estrogen and Progesterone on the ACL and AT
LONG TITLE: The Effects of Supplemental Estrogen and Progesterone on the Anterior Cruciate Ligament (ACL) and Achilles Tendon (AT)

AIDS:	N	TOTALS	A	B	D
		Inpatient	0	0	0
START DATE:	11/25/2003	Scatter Bed	0	0	0
Total # pts expected for entire study:	18	Outpatient	43	0	0
		Scatter RN Hours	0	0	0
		Offsite Visits	0	0	0

RESEARCH BIONUTRITION	N	MULTICENTER STUDY	N
INFORMATICS CORE	Y	CLINICAL TRIAL	N
BIostatistician	N	CORE LAB	Y
ANCILLARIES ONLY	N		

INVESTIGATOR	DEPARTMENT	NON-HOST INSTITUTION: STATE, COUNTRY
TROJIAN, THOMAS MD	MEDICINE/FAMILY MEDICINE	ST. FRANCIS HOSPITAL, CT USA
DIPASQUALE, CHRIS PHD	KINESIOLOGY	UCONN - STORRS, CT USA

SUBPROJECT DESCRIPTION:

Anterior cruciate ligament (ACL) tears are a major health risk for female athletes. Early degenerative arthritis of the knee is more likely to develop in women with ACL tears as compared to their uninjured counterparts. ACL tears normally produce 6 - 12 months of disability after the injury. The National Collegiate Athletic Association Injury Surveillance Survey data identifies that female college athletes have a 3 - 8 times higher rate of ACL tears compared to males. ACL tears produce immediate and delayed disability in women.

Little is known about modifiable risk factors in the prevention of ACL tears. Discovering these factors has been identified as a major goal by the National Institute of Arthritis Musculoskeletal and Skin Diseases (NIAMS) and the Office of Research on Women's Health. There are a number of proposed risk factors for instance a proposed association between ACL tears and the menstrual cycle. Over the menstrual cycle, changes are seen in the ACL measurements. The fluctuation of estrogen levels are proposed to be the cause of the changes in the ACL properties. Muscle-tendons complexes, including the Achilles tendon (AT), provide additional stability to the knee joint. These secondary restraints play an important role in the stability of the knee. Estrogen and progesterone affect the collagen content of tendons and ligaments (like the ACL and AT). Some investigators have recommended oral contraceptives, which prevents the estrogen spike, in order to prevent injury. These recommendations are premature since ACL risk factors have not been thoroughly studied and any current recommendations for the use of oral contraceptives are from retrospective studies with small sample sizes.

Further, prospective, adequately powered, studies are needed to define the affects of supplemental hormones such as oral contraceptives (OCP) on the stretch and strain properties of the ACL. Previous studies quantifying the change in ACL laxity measurements across the menstrual cycle while a woman is on OCPs do not exist.

The specific aims of the proposed research project are first, to identify the affects of a monophasic OCPs on ACL measurements across the menstrual cycle. The secondary aim of the proposed research project is to identify the affects of monophasic OCPs on tendon extensibility across the menstrual cycle. Lastly, the proposed project will be used as preliminary data for a cross-over study investigating the change in ACL measurements with and without OCPs in an RO3 or RO1 application to NIAMS, which will carry out a more comprehensive evaluation on the risk factors for ACL tears.

SUBPROJECT PROGRESS:

We have 11 total with 6 new since 4/1/2006. We have tried newspaper, posters at health clubs, and other methods of recruitment but only get responses from the Broadcast E-mail message. There has been no unexpected safety concerns. No injury to participants has occurred. We have no interim data since the blood work is being batched analyzed. We will need to request an extension to the time frame. No publications from this study. We were mentioned in celebrating women and GCRC was mentioned.

SPID: 0536 **PROTOCOL:** 536 **TYPE:** RESEARCH

SHORT TITLE: Effects of Aripiprazole on Subjective and Physiological Responses to Alcohol

LONG TITLE: Effects of Aripiprazole on Subjective and Physiological Responses to Alcohol

AIDS:	N	TOTALS	A	B	D
			Inpatient	0	0
START DATE:	12/1/2003	Scatter Bed	0	0	0
Total # pts expected for entire study:	20	Outpatient	39	0	0
		Scatter RN Hours	0	0	0
		Offsite Visits	0	0	0

RESEARCH BIONUTRITION	N	MULTICENTER STUDY	N
INFORMATICS CORE	N	CLINICAL TRIAL	N
BIostatistician	Y	CORE LAB	Y
ANCILLARIES ONLY	N		

INVESTIGATOR	DEPARTMENT	NON-HOST INSTITUTION: STATE, COUNTRY
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KRANZLER, HENRY R MD	PSYCHIATRY	
COVAULT, JONATHAN MD, PHD	Psychiatry	
HERNANDEZ-AVILA, CARLOS MD	Psychiatry	
ONCKEN, CHERYL MD	Medicine	
PIERUCCI, AMIRA PHD	Psychiatry	

SUBPROJECT DESCRIPTION:

A. 1. Specific Aims:

To study the effect of aripiprazole on behavioral effects (i.e., sedative/hypnotic, anxiolytic, stress-reducing properties) and physiological effects (i.e., blood pressure, heart rate, psychomotor task performance) of a moderate dose of alcohol in 20 healthy subjects with no history of alcohol abuse or dependence. Genetic analysis will also provide preliminary information on allelic association both to alcohol response in healthy individuals and as control data for studies of individuals affected with alcohol and/or drug dependence.

2. Hypothesis:

Aripiprazole is a new atypical antipsychotic with a unique receptor binding profile that combines partial agonist activity at D2 and 5-HT1A receptors and potent antagonism at 5-HT2A receptors. Based on this profile of activity, we hypothesize that aripiprazole will reduce the pleasurable, stimulating, and anxiolytic effects of alcohol, but not its effects on blood pressure and heart rate. An evaluation of this hypothesis may help to elucidate the neuropsychopharmacology of alcohol and may suggest a novel approach to the pharmacotherapy of alcohol dependence.

SUBPROJECT PROGRESS:

A total of 14 subjects were enrolled into the study during the report period (a total of 49 since initiation of the study). Subject enrollment into the study began in June 2005 and was completed in December 2006. A total of 20 subjects have completed all three laboratory sessions for the study. The last subject completed full study participation in January 2007. During the report period, a few modifications to the protocol were made. Joel Gelernter, Xingguang Luo, and Yang Bao-zhu were added as co-investigators of the study, and Dr. Demartines was removed as co-investigator. The Informed Consent Form B was removed because blood is drawn for all subjects enrolled into the study. Approval was granted to increase enrollment of subjects from 50 to 60, so as to account for subjects who were screen failures, withdrew from study, or who did not complete study visits and in order for 20 subjects to complete all three lab sessions. Although recruitment plans for this study did not change during the report period, approval was granted to ask individuals who have been phone screened and determined ineligible for this study whether they want to be informed of other currently available studies within our clinic that they may qualify for. Enrollment has ended and the study is currently under data analysis. There were no unexpected safety concerns associated with this study. The medication and alcohol were well tolerated and there were no serious adverse events. The profile of observed adverse events does not differ substantially from that expected at the onset of the study. Additional genotyping is anticipated (use of GCRC Core lab), suggesting 28 sample with 10 markers each. The manuscript for this study will be submitted for publication, and will cite GCRC support.

SPID: 0538 **PROTOCOL:** 538 **TYPE:** RESEARCH

SHORT TITLE: Combination Nicotine Replacement for Alcoholic Smokers

LONG TITLE: Combination Nicotine Replacement for Alcoholic Smokers

AIDS:	N	TOTALS	A	B	D
		Inpatient	0	0	0
START DATE:	12/18/2003	Scatter Bed	0	0	0
Total # pts expected for entire study:	175	Outpatient	0	0	0
		Scatter RN Hours	0	0	0
		Offsite Visits	0	0	0

RESEARCH BIONUTRITION	N	MULTICENTER STUDY	N	
INFORMATICS CORE	Y	CLINICAL TRIAL	Y	Phase II
BIostatistician	N	CORE LAB	N	
ANCILLARIES ONLY	N			

INVESTIGATOR	DEPARTMENT	NON-HOST INSTITUTION: STATE, COUNTRY
LITT, MARK D PHD	BEHAVIORAL SCI & COMM HLTH	
COONEY, JUDITH PHD	MEDICINE	YALE UNIVERSITY, CT USA
COONEY, NED L PHD	PSYCHIATRY	YALE UNIVERSITY, CT USA
ONCKEN, CHERYL MD	Medicine	

SUBPROJECT DESCRIPTION:

Objectives of the project. Tobacco use among alcoholic patients is a major public health problem. The broad objective of this study is to develop recommendations for empirically supported smoking cessation treatment for alcohol dependent smokers in the initial phase of outpatient alcohol treatment. The specific aims are to: (1) compare the efficacy of smoking cessation treatment using nicotine replacement therapy (NRT) consisting of active nicotine patch and active nicotine gum (Combination NRT) versus therapy consisting of active nicotine patch and placebo nicotine gum (Single NRT) in a sample of alcohol dependent tobacco smokers in an early phase of alcohol treatment; and (2) determine whether smoking status is a mediator of drinking outcomes. In addition to one-year outcome assessments, in vivo process assessments will be collected using an Electronic Diary (ED). This ED process data will be used to: (3) compare the effects of Single versus Combination NRT on frequency and intensity of urge to smoke and urge to drink; (4) determine the impact of nicotine gum self-administration on subsequent momentary urge to drink and urge to smoke using electronic diary data; and (5) determine the momentary triggers for nicotine gum self-administration

SUBPROJECT PROGRESS:

0 Patients enrolled in reporting period; 132 enrolled in study. No changes in recruitment plans needed; recruitment finished. No unexpected safety concerns. No interim data available at this time. No changes proposed or anticipated in protocol. No publications available yet.

SPID: 0540	PROTOCOL: 540	TYPE: RESEARCH
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SHORT TITLE: PACTG 1025

LONG TITLE: Pediatric AIDS Clinical Trial Group (PACTG) 1025: Perinatal Core Protocol for HIV-infected Pregnant Women

AIDS:	Y	TOTALS	A	B	D
		Inpatient	0	0	0
START DATE:	1/15/2004	Scatter Bed	0	0	0
Total # pts expected for entire study:	5	Outpatient	3	0	0
		Scatter RN Hours	0	0	0
		Offsite Visits	0	0	0

RESEARCH BIONUTRITION	N	MULTICENTER STUDY	Y	
INFORMATICS CORE	Y	CLINICAL TRIAL	Y	Phase IV
BIostatistician	N	CORE LAB	N	
ANCILLARIES ONLY	N			

INVESTIGATOR	DEPARTMENT	NON-HOST INSTITUTION: STATE, COUNTRY
SALAZAR, JUAN C MD	PEDIATRICS	
FEDER, HENRY MD	Medicine/Family Medicine	
KRAUSE, PETER MD	Pediatrics	

SUBPROJECT DESCRIPTION:

PACTG P1025 is a prospective cohort study that provides a framework for collection and evaluation of data and collection of repository specimens from Human Immunodeficiency Virus (HIV)-infected pregnant and postpartum women and their infants. The primary objectives of this study are: to assess the effectiveness of interventions (e.g. antiretroviral therapy and mode of delivery) prescribed for prevention of vertical transmission of HIV and/or for women's health; to assess material and infant safety of interventions (e.g. Antiretroviral Therapy (ART) and mode of delivery) prescribed for women's health and/or for prevention of vertical transmission of HIV; to provide a framework and specimen repository for intensive substudies (such as PACTG P1026s, pharmacokinetics in pregnancy), New Works Concept Sheets (NWCS) and Data Analysis Concept Sheets (DACS) that aim to further elucidate risk factors for and mechanisms of vertical transmission of HIV, as well as factors that affect maternal and infant outcomes; to assess adherence to ART among HIV-infected pregnant women during pregnancy and postpartum and its impact on women's health and vertical transmission, and to assess adherence to chemoprophylaxis in infants.

SUBPROJECT PROGRESS:

PACTG 1025 (Version 3.0) has had a total of two enrollments the only enrollments represent the only enrollments on this study since initiation.

Due to funding changes throughout the PACTG/IMPACT Network, we will no longer be able to offer this protocol.

SPID: 0541	PROTOCOL: 541	TYPE: RESEARCH
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SHORT TITLE: PACTG 1026S

LONG TITLE: Pediatric AIDS Clinical Trial Group (PACTG) 1026S: Pharmacokinetic Properties of HIV Antiretroviral Drugs During Pregnancy

AIDS:	Y	TOTALS	A	B	D
		Inpatient	0	0	0
START DATE:	1/15/2004	Scatter Bed	0	0	0
Total # pts expected for entire study:	5	Outpatient	0	0	0
		Scatter RN Hours	0	0	0
		Offsite Visits	0	0	0

RESEARCH BIONUTRITION	N	MULTICENTER STUDY	Y	
INFORMATICS CORE	Y	CLINICAL TRIAL	Y	Phase IV
BIostatistician	N	CORE LAB	N	
ANCILLARIES ONLY	N			

INVESTIGATOR	DEPARTMENT	NON-HOST INSTITUTION: STATE, COUNTRY
SALAZAR, JUAN C MD	PEDIATRICS	
FEDER, HENRY MD	Medicine/Family Medicine	
KRAUSE, PETER MD	Pediatrics	

SUBPROJECT DESCRIPTION:

This is a prospective pharmacokinetics (PK) study to evaluate the pharmacokinetics of currently prescribed antiretroviral drugs and interacting combinations of these drugs in pregnant Human Immunodeficiency Virus (HIV)-infected women. The primary objective is to describe the pharmacokinetic (PK) parameters during pregnancy of selected antiretroviral women, and to determine if therapeutic dosing regimens of these antiretroviral drugs produce adequate drug exposure during pregnancy compared to a) historical data from non-pregnant adults and b) the same women in the study cohorts during the post partum period.

SUBPROJECT PROGRESS:

PACTG 1026s (Version 5.0) There have been no enrollments over the report period, as well as since the initiation of the study.

Due to funding changes throughout the PACTG/IMPAACT Network, we will no longer be able to offer this protocol.

SPID: 0542	PROTOCOL: 542	TYPE: RESEARCH
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SHORT TITLE: Effect of Letrozole on bone markers and blood pressure

LONG TITLE: Short term Effects of Letrozole on Bone Markers and Vascular Indices in Postmenopausal Women after Completion of Tamoxifen Therapy for Primary Breast Cancer

AIDS:	N	TOTALS	A	B	D
			Inpatient	0	0
START DATE:	2/10/2004	Scatter Bed	0	0	0
Total # pts expected for entire study:	8	Outpatient	30	0	0
		Scatter RN Hours	0	0	0
		Offsite Visits	0	0	0

RESEARCH BIONUTRITION	N	MULTICENTER STUDY	N
INFORMATICS CORE	Y	CLINICAL TRIAL	N
BIostatistician	N	CORE LAB	Y
ANCILLARIES ONLY	N		

INVESTIGATOR	DEPARTMENT	NON-HOST INSTITUTION: STATE, COUNTRY
TAXEL, PAMELA MD	Medicine	
MIRZA, FARYAL MD	Medicine	
MOYO, VICTOR MD	Medicine/Oncology	
TANNENBAUM, SUSAN MD	Medicine/Hem-Onc	

SUBPROJECT DESCRIPTION:

Studies using aromatase inhibitors (AI) have recently demonstrated improved disease free survival after five years of tamoxifen therapy for early stage breast cancer in postmenopausal women. AI are a class of compounds that inhibit the synthesis of estrogens from androgens by blocking aromatase, a cytochrome P450 enzyme, which catalyzes the peripheral conversion of androgens to estrogens, thereby reducing the tissue and plasma concentration of estradiol to below castrate levels.

We hypothesize that with suppression of estradiol, letrozole, the most potent aromatase inhibitor, will cause a significant increase in markers of bone resorption and bone formation, along with an increase in baseline blood pressure and loss of nocturnal dipping of blood pressure. The following specific aims will be studied:

To determine the effects of letrozole on sex hormone levels and the relationship of change in sex hormone levels to the change in bone markers.

To determine the change in markers of bone resorption and formation.

To examine the effects of letrozole on 24 hr ambulatory blood pressure monitoring and office blood pressure.

To determine change in parameters of neurocognitive function with letrozole therapy.

This will be a 12 week, open label pilot study evaluating women with primary breast cancer, who have completed five years of tamoxifen treatment and are opting to choose letrozole as treatment in consultation with their oncologist. The patients will serve as their own controls.

SUBPROJECT PROGRESS:

Total number of subjects in the study entered to date is 9. 4 subjects were enrolled in the reporting period. As we have blood pressure data only on 8 patients, we still need to recruit 2 more patients to have blood pressure data on a total of 10 patients. There have been no interim safety concerns as no intervention is involved. Data is in the process of being compiled and data entry process has already been initiated. There have been no publications to date.

SPID: 0546	PROTOCOL: 546	TYPE: RESEARCH
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SHORT TITLE: Access to Oral Care

LONG TITLE: A Feasibility Study of New Technology on Access to Oral Health Care

AIDS:	N	TOTALS	A	B	D
		Inpatient	0	0	0
START DATE:	3/30/2004	Scatter Bed	0	0	0
Total # pts expected for entire study:	100	Outpatient	0	0	0
		Scatter RN Hours	0	0	0
		Offsite Visits	0	0	0

RESEARCH BIONUTRITION	N	MULTICENTER STUDY	N
INFORMATICS CORE	Y	CLINICAL TRIAL	N
BIostatistician	N	CORE LAB	N
ANCILLARIES ONLY	N		

INVESTIGATOR	DEPARTMENT	NON-HOST INSTITUTION: STATE, COUNTRY
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ROSSOMANDO, EDWARD F DDS, MS, PHD	Biostructure & Function	
BENITEZ, HUBERT DDS, MHA	Biostructure & Function	
LALLA, RAJESH V BDS, PHD	ORAL DIAGNOSIS	
PETERSON, DOUGLAS DMD, PHD	Oral Diagnostics	

SUBPROJECT DESCRIPTION:

Given the conclusion of the Surgeon General's Report on Oral Health In America that all our citizens do not have equal access to dental services, the American Dental Trade Association (ADTA)/Santa Fe initiative to support research programs to investigate possible causes for this inequity is most welcome. While the research from their initiative is likely to identify numerous causes, one of the most prevalent may be the lack of information on the part of the public concerning the importance of oral health and of the necessity of regular oral health examinations. However, a recent study by Alfano and Horowitz suggests that when presented with information about the prevalence of oral cancer, the public will visit a dentist.

This finding, taken together with the availability of a new product for the testing of oral cancer, a brush biopsy called OralCDx, suggests an opportunity to test the hypothesis that an educational campaign designed to raise public awareness of the life threatening statistics on oral cancer together with the message that oral cancer screening is available at a local dental clinic will result in visits to dentists by those members of the public who do not regularly seek access to dental services. A corollary to this hypothesis is that a given number of those that seek the free screenings, when informed of the need for additional services to soft and hard oral tissues, will remain with the practice to obtain these services.

In this proposal we describe a feasibility study, which begins with an educational campaign to inform the public of the incidence of oral cancer and to offer a screening for oral cancer. The aim will be to entice new patients to obtain oral cancer screening. At the testing site, the OralCDx test will be used for screening of oral lesions identified during the examination. In addition, as part of the study, each patient will receive a full mouth examination of hard and soft tissues and, when appropriate, will be advised of the need for additional dental services.

The project will: 1) track the number of new patients that seek the oral cancer test in response to the campaign, 2) track the number of patients with an oral lesion 3) track the results of the OralCDx brush biopsy 4) track the number of patients that return for additional services. 5) For those patients with an abnormal brush biopsy result who have a scalpel biopsy subsequently, compare the results of the brush biopsy and scalpel biopsy. At the conclusion of the 3-6 month study period, the number of returnees as a result of the oral screening examination will be compiled and reported. An increase in this number will support the hypothesis that connecting oral health to a potentially life-threatening disease such as oral cancer can increase utilization of oral health services.

SUBPROJECT PROGRESS:

Since filing the last report, there has been no activity on this project.

SPID: 0548 **PROTOCOL:** 548 **TYPE:** RESEARCH

SHORT TITLE: Chronic Recidivist Alcohol-Dependent Patients
LONG TITLE: Contingency Management for Chronic Recidivist Alcohol-Dependent Patients

	AIDS:	Y	TOTALS	TOTALS		
				A	B	D
			Inpatient	0	0	0
START DATE:		4/7/2004	Scatter Bed	0	0	0
Total # pts expected for entire study:		116	Outpatient	0	0	0
			Scatter RN Hours	0	0	0
			Offsite Visits	124	0	0

RESEARCH BIONUTRITION	N	MULTICENTER STUDY	N
INFORMATICS CORE	Y	CLINICAL TRIAL	N
BIostatistician	N	CORE LAB	N
ANCILLARIES ONLY	N		

INVESTIGATOR	DEPARTMENT	NON-HOST INSTITUTION: STATE, COUNTRY
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PETRY, NANCY M PHD	PSYCHIATRY	
BABOR, THOMAS F PHD	COMMUNITY MEDICINE	
KADDEN, RONALD M PHD	Psychiatry	

SUBPROJECT DESCRIPTION:

In a pilot study from our previous granting period, we demonstrated the efficacy of a relatively low-cost contingency management (CM) procedure for retaining alcohol-dependent patients in treatment and reducing alcohol as well as other drug use (Petry et al., 2000). This study will extend use of these procedures to chronic recidivist alcohol-dependent patients and evaluate their efficacy for reducing in-patient detoxification services. Specifically, 116 alcohol-dependent patients who have received 4 or more alcohol detoxifications in a calendar year will be randomly assigned to one of two 6-month treatment conditions: standard case management treatment, or standard case management treatment plus CM. In the CM condition, patients earn the chance to win prizes by submitting negative breath samples and by complying with steps toward treatment goals, such as attending outpatient substance abuse treatment services, attending appointments with low income housing programs, or complying with outpatient psychiatric treatment. Treatment services received, alcohol and drug use, psychosocial functioning, and Human Immunodeficiency Virus (HIV) risk behaviors will be measured pre-treatment and at months 1, 3, and 6 (post-treatment), and at follow-ups scheduled for 9, 12, and 18 months after intake.

Compared to standard case management treatment, we expect that those assigned to the CM condition will decrease alcohol consumption and present for fewer inpatient detoxifications, while showing greater engagement and retention in outpatient treatment. We also anticipate improvements in psychosocial functioning and decreases in HIV risk behaviors in the CM group. Patient characteristics that may be associated with a positive response to treatment will be assessed. We will also evaluate the cost-effectiveness of this CM intervention in relation to standard case management services.

SUBPROJECT PROGRESS:

Total Enrollment: 102 Past Year Enrollment: 14 · No changes in recruitment plans are needed. · No unexpected safety concerns have occurred. · Interim data and outcomes are not available. · Changes to protocol: 1) Updated the protocol's version date to 12/06 in order to facilitate study administration. 2) Updated the protocol with an updated listed of study sites: Alcohol and Drug Recovery Center, Hartford, CT; Blue Hills Hospital, Hartford, CT (Department of Mental Health and Addiction Services); Capitol Region Mental Health Center, Hartford, CT (Department of Mental Health and Addiction Services); Carlson Recovery Center, Springfield, MA (Baystate Medical Center); Connecticut Mental Health Center, New Haven, CT; Morris Foundation, Waterbury, CT; St. Mary's Hospital, Waterbury, CT and the University of Connecticut Health Center. 3) Corrected typographical errors discovered in the protocol. 4) Added the DSM-IV alcohol abuse and dependence measure, as well as the Diagnostic and Statistical Manual of Mental Disorders - Fourth Edition (DSM-IV) measure for opiate abuse and dependence, to the Assessments section of the protocol. · No publications since previous annual report.

SPID: 0549	PROTOCOL: 549	TYPE: RESEARCH
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SHORT TITLE: GABRA2

LONG TITLE: Haplotype Association Study of the GABRA2 Gene and Alcohol Dependence in Project MATCH Subjects

AIDS:	N	TOTALS	A	B	D
			Inpatient	0	0
START DATE: 3/18/2004		Scatter Bed	0	0	0
Total # pts expected for entire study:	2,200	Outpatient	1	0	0
		Scatter RN Hours	0	0	0
		Offsite Visits	0	0	0

RESEARCH BIONUTRITION	N	MULTICENTER STUDY	N
INFORMATICS CORE	N	CLINICAL TRIAL	N
BIostatistician	N	CORE LAB	Y
ANCILLARIES ONLY	N		

INVESTIGATOR	DEPARTMENT	NON-HOST INSTITUTION: STATE, COUNTRY
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COVAULT, JONATHAN MD, PHD	Psychiatry	
GELERNTER, JOEL E MD	PSYCHIATRY	YALE UNIVERSITY, CT USA
HESELBROCK, VICTOR M PHD	PSYCHIATRY	
KRANZLER, HENRY R MD	PSYCHIATRY	

SUBPROJECT DESCRIPTION:

Alcohol dependence is a highly prevalent disorder that is associated with serious morbidity and mortality. Alcohol dependence has a significant heritable component estimated to account for 50-60% of risk. We have recently used a Connecticut sample of 258 Caucasian alcohol dependent and 335 screened controls to confirm an association of alcohol dependence with the GABRA2 gene reported in an abstract at the Research Society on Alcoholism in 2003. We found a 7% excess frequency (44% vs. 37%) of a seven-marker haplotype extending 98,000 bp over the 3'-half of the GABRA2 gene for subjects with alcohol dependence.

We are now proposing to extend our case control association investigations of the GABRA2 gene and alcoholism by examining a more diverse multi-center sample of 1100 alcoholic subjects collected in project MATCH (a multi-center alcoholism treatment trial) with a collection of 1100 control subjects. We will use this sample to extend our observations in several ways: i) to test for the association in a larger and more geographically diverse sample, ii) to use additional markers to better define the 3'-endpoint of association, iii) potentially focus the area of association by use of a larger and more genetically diverse sample iii) to examine for association with subtypes of alcohol dependent phenotype and co-morbid conditions. We will use the Duffy antigen as an initial screen for differences in Caucasian versus Black chromosome admixture in the MATCH versus control sample from the NYC Cancer Project. If significant differences are detected we will plan to collaborate with Dr. Joel Gelernter at Yale whose laboratory has developed techniques using a panel of racially informative markers to allow statistical correction case-control genetic associations.

A second aim will be to examine human GABRA2 Carrier Deoxyribonucleic Acid (cDNA) clones for splice or coding sequence changes in linkage with a known exon 4 synonymous Single nucleotide polymorphism (SNP) present at higher frequency in alcoholics in our initial sample.

SUBPROJECT PROGRESS:

GCRC Annual report April 1, 2006 March 31, 2007 Protocol: GCRC 549 - Haplotype association study of the GABRA2 gene and alcohol dependence in project MATCH subjects. PI: Jonathan Covault 1) Number of subjects enrolled during the report period: N/A since initiation of study: N/A (this study uses blood samples collected from subjects enrolled in a multicenter NIH alcohol treatment study 'Project MATCH' several years ago as well as cases and controls collected at UCHC as part of other studies of alcohol dependence) 2) Planned changes in recruitment plans: n/a 3) Unexpected safety concerns and their resolution: None occurred. 4) Interim data: SNP genotyping has been completed on 800 project MATCH together with 600 control and 600 alcoholic cases from central Connecticut at 8 SNPs in the GABRA2 gene, 4 SNPs in the adjacent GABRG1 gene and 3 SNPs in the intergenic region. Results from indicate the markers in these two genes are both associated with diagnosis of alcohol dependence, but with greater effect size for markers in the GABRG1 gene. The results are not explained linkage disequilibrium between markers in the two genes, although there is moderate linkage between the two haplotype blocks in the two genes. 5) Proposed changes made or anticipated in the

protocol: None; Publications citing the GCRC support for this study: Covault, J., Gelernter, J., Jensen, K., Anton, R., and Kranzler, H.R., (2007) Markers in the 5'Region of GABRG1 Associate to Alcohol Dependence and are in Linkage Disequilibrium with Markers in the Adjacent GABRA2 Gene. *Neuropsychopharmacology* (in press).

SPID:	0551	PROTOCOL:	551	TYPE:	RESEARCH	
SHORT TITLE:	ILIAD					
LONG TITLE:	Idiosyncratic Liver Injury Associated With Drugs: A Retrospective Study					
AIDS:	N	TOTALS		A	B	D
		Inpatient		0	0	0
START DATE:	4/29/2004	Scatter Bed		0	0	0
Total # pts expected for entire study:	160	Outpatient		2	0	0
		Scatter RN Hours		0	0	0
		Offsite Visits		0	0	0
RESEARCH BIONUTRITION	N	MULTICENTER STUDY		Y		
INFORMATICS CORE	Y	CLINICAL TRIAL		N		
BIostatistician	N	CORE LAB		Y		
ANCILLARIES ONLY	N					

INVESTIGATOR	DEPARTMENT	NON-HOST INSTITUTION: STATE, COUNTRY
BONKOVSKY, HERBERT L MD	MEDICINE/GASTROENTEROLOGY	
FRESTON, JAMES MD	Medicine	
ROSSON, ROBERT MD	Medicine	

SUBPROJECT DESCRIPTION:

Background and Rationale: Drug induced liver injury (DILI) is the single most common reason for regulatory actions concerning drugs, including failure to gain approval for marketing, removal from the market place, and restriction of prescribing indications. DILI is also a significant cause of morbidity and mortality in many patient populations. To stimulate and facilitate research into DILI, the National Institute of Diabetes, Digestive and Kidney Diseases (NIDDK) has recently established the Drug-Induced Liver Injury Network (DILIN). One of the initial projects to be conducted by the network is to retrospectively establish a nationwide registry of patients who have suffered severe idiosyncratic liver injury associated with drugs (ILIAD), and to collect, immortalize and store serum, Deoxyribonucleic acid (DNA), and lymphocytes from these patients (hereafter referred to as the "ILIAD protocol"). This ILIAD protocol will serve as a resource for subsequent mechanistic investigations of the basis for susceptibility to severe idiosyncratic DILI.

Specific Aims and Objectives: The primary goal of the ILIAD protocol is to create: (a) a clinical database consisting of individuals who have experienced severe DILI caused by four specific drugs, and the relevant clinical data concerning the episode of DILI; and, (b) to create a bank of biological specimens obtained from these individuals. Corresponding information from control subjects will also be collected. These biological specimens will be DNA, plasma, and immortalized lymphocytes. Immortalized lymphocytes will provide unlimited amounts of genomic DNA for study as well as living immune cells for phenotyping studies. A secondary goal of the ILIAD protocol is to maintain a registry of cases in the ILIAD database so that they may be recontacted in the future. It is expected that this will facilitate additional studies exploring the mechanisms of DILI.

Targeted Drugs: The initial drugs to be targeted in the ILIAD protocol are isoniazid (INH), phenytoin, clavulanic acid / amoxicillin (Augmentin and valproic acid. For INH, phenytoin, or clavulanic acid / amoxicillin, severe liver injury is defined as a documented serum total bilirubin > 2.5 mg/dl; for valproic acid, the criteria are compatible symptomatic clinical presentation that is severe enough to prompt hospitalization and evidence of liver dysfunction International normalized ratio (INR) > 1.5 or Alanine transaminase (ALT) > 3 X Upper Limit of Normal (ULN), and/or characteristic liver biopsy). The target drugs were chosen because they cause severe DILI at a high rate compared with other drugs, making our target enrollment for each drug (n = 50-100) attainable. In addition, these drugs are frequently administered to reasonably healthy patients not concurrently receiving other drugs more likely to be hepatotoxic, facilitating causation assessment.

Basic Study Design: The five DILIN clinical centers will identify and contact patients at their own and affiliated institutions who may have suffered a liver injury due to one of the targeted drugs. They will also contact gastroenterologists, hepatologists, and other health care professionals most likely to have treated DILI cases. In the latter case, an information packet will be sent by the treating physician to the potential subject, and interested subjects will be requested to contact one of the five clinical sites. In either case, the subject will be given a brief description of the study's purpose and procedures, and when further interest in the study is expressed, s/he will be mailed provided with an information packet including the informed consent document, The Health Insurance

Portability and Accountability Act (HIPAA) authorization and release of medical record forms. Once these documents have been received reviewed by the subject, study staff will contact the potential subject by telephone a second time. This follow-up contact will either occur by telephone or in person at the subject's convenience. Informed consent will be obtained, and if this occurs over the telephone, it will be witnessed by a third party on the line. Then, requisite information will be collected using a telephone or personal interview format. Prior to ending this phone call the end of the second contact, the subject will be asked to sign the consent, HIPAA authorization, and release of medical information forms and return provide them to the DILIN clinical site. Arrangements for blood drawing will be made. The blood sample will be shipped to the Rutgers University Cell and DNA Repository (RUCDR) where DNA will be extracted and lymphocytes will be immortalized. DNA, plasma and immortalized lymphocytes will be frozen and stored for future studies. Once the signed documents have been received, medical records and charts will also be retrieved from the appropriate health care provider(s). Detailed clinical information concerning the DILI event will be abstracted from the charts and entered onto case report forms. This information will then be reviewed by the DILIN Causality Committee, and it will make the final determination on whether the patient was a true DILI case.

SUBPROJECT PROGRESS:

There are a total of eight subjects enrolled into this study. Two were enrolled during the current report period. There are no changes in recruitment plans at this time. In addition, there are no unexpected safety concerns to report. The following are the modification submitted to the Institutional Review Board (IRB) none of these changes imposed an increases the risk to subjects: 1) A letter that we would like to send via registered mail to patient who we are unable to contact over the phone. 2) In the thank you letter, for sending out the copy of the signed Informed Consent Form (ICF) and a lab kit bullet #3) regarding the stipend was removed to be consistent with the protocol. As well as the removal of the following Co-Investigators Dr. Siddiqui, Dr. Aziz and Dr. Wu.

SPID: 0553 **PROTOCOL:** 553 **TYPE:** RESEARCH

SHORT TITLE: The Relationship Between Functional Independence, Quality of Life and Parental
LONG TITLE: The Relationship Between Functional Independence, Quality of Life and Parental Stress for Adolescents with
 Developmental Disabilities

AIDS:	N	TOTALS	A	B	D
			Inpatient	0	0
START DATE:	6/1/2004	Scatter Bed	0	0	0
Total # pts expected for entire study:	100	Outpatient	0	0	0
		Scatter RN Hours	0	0	0
		Offsite Visits	0	0	0

RESEARCH BIONUTRITION	N	MULTICENTER STUDY	N
INFORMATICS CORE	Y	CLINICAL TRIAL	N
BIostatistician	Y	CORE LAB	N
ANCILLARIES ONLY	N		

INVESTIGATOR	DEPARTMENT	NON-HOST INSTITUTION: STATE, COUNTRY
LEGER, ROBIN PHD, RN	Orthopedics	
SPENCER, TAYLOR BS	Medicine	
THRALL, ROGER S PHD	MEDICINE/PULMONARY	

SUBPROJECT DESCRIPTION:

The federal Developmental Disabilities Act defines a developmental disability as "a severe, chronic disability that is attributable to a mental or physical impairment or a combination of mental or physical impairments 1." Applicable medical conditions include but are not limited to spina bifida, cerebral palsy, muscular dystrophy, mental retardation, and fetal alcohol syndrome. These diverse conditions may result in significant limitations in major life activities such as self-care, expression, learning, mobility, independent living, and economic self-sufficiency. In spite of such health-related limitations, maximizing health-related quality of life is an ultimate goal of the health care profession for this population (as it is for patients in general).

SUBPROJECT PROGRESS:

This is the research project of a graduate student, Taylor Spencer, which is in its third year. His mentors are Dr. Roger Thrall and Dr. Robin Leger (PI). A total of 72 youth have been enrolled in the study, 66 for the quantitative portion and 6 for the qualitative portion. There are no new additional analyses to the quantitative portion. The 6 qualitative interviews conducted by Taylor Spencer have been transcribed and are lengthy. They are currently undergoing a cursory preliminary analysis for major themes under the guidance and with the consultation of Dr. Linda Wagner.

Taylor Spencer is opting for a 5th year at medical school & in the Masters in Public Health (MPH) program. We will keep the study open with the UCHC Institutional Review Board (IRB) for an additional year which will primarily focus on continued enrollment to the qualitative portion and qualitative analyses.

SPID:	0554	PROTOCOL:	554	TYPE:	RESEARCH	
SHORT TITLE:	Emergency Department Alcohol Screening Project					
LONG TITLE:	Emergency Department Alcohol Screening Project					
AIDS:	N	TOTALS		A	B	D
		Inpatient		0	0	0
START DATE:	5/11/2004	Scatter Bed		0	0	0
Total # pts expected for entire study:	1,400	Outpatient		0	0	0
		Scatter RN Hours		0	0	0
		Offsite Visits		0	0	0
RESEARCH BIONUTRITION	N	MULTICENTER STUDY		Y		
INFORMATICS CORE	Y	CLINICAL TRIAL		N		
BIostatistician	N	CORE LAB		N		
ANCILLARIES ONLY	N					

INVESTIGATOR	DEPARTMENT	NON-HOST INSTITUTION: STATE, COUNTRY
ASELTINE, ROBERT H PHD	BEHAVIORAL SCI & COMM HLTH	
JAMES, AMY PHD	Behavioral Sci & Comm Hlth	

SUBPROJECT DESCRIPTION:

There are approximately 100 million visits to Emergency Departments (EDs) each year. As many as 30% of these ED patients present with alcohol related problems. Among ED patients, 22-31% screen positively on the CAGE instruments (>2 questions), more than 10% of patients meet Diagnostic and Statistical Manual of Mental Disorders (DSM-IV) or International Classification of Diseases 10th Edition (ICD-10) criteria for alcohol dependence, and 25% are Alcohol Use Disorders Identification Test (AUDIT) positive using a probability sample. ED patients are 1.5-3 times more likely than primary care patients to report heavy drinking, consequences of drinking, alcohol dependence, or treatment for an alcohol problem. In a five year follow-up, alcohol intoxicated ED patients had twice the mortality rate as the non-intoxicated comparison group. If 10% of ED patients meet criteria for dependence and 20% meet criteria for CAGE >2, then one might estimate conservatively that the outcome of 10 million ED visits could be improved by treatment contact. This is the rationale for the Connecticut state mandate for ED screening. Among persons identified with at-risk drinking in the ED setting, Screening, Brief Intervention, Referral and Treatment (SBIRT) counseling will result in a significantly decreased frequency and quantity of self-reported alcohol use, reduced alcohol related health risk factors, and increased completion of referrals in the intervention group at 3 and 6 month follow up, compared to a control group that receives only written advice. At-risk drinking is a major source of preventable morbidity and mortality in the U.S. SBIRT has been shown to be an effective modality for eliminating or reducing harmful health behaviors related to alcohol abuse, but these techniques are poorly known and little used by ED providers, who see the consequences of alcohol abuse on a daily basis but lack knowledge and skills to take advantage of the teachable moment in the ED to engage patients in health promoting behavior change. Through a multi-center consortium of academic ED's in support of the NASD initiative, an opportunity is available to encourage screenings for at-risk alcohol consumption among individuals presenting for care in the emergency department setting. We therefore propose to conduct a two-year pilot study to evaluate the efficacy of a SBIRT designed for ED patients in the context of National Alcohol Screening Day (NASD).

SUBPROJECT PROGRESS:

This study has been closed to enrollment, data analysis for the 6 and 12 month follow-up is currently underway, manuscripts are in preparation for the 3 month results. Objectives. This study examined the impact of an intervention program (SBIRT) designed to facilitate changes in at-risk and dependent drinking behavior in emergency department (ED) patients using motivational intervention that has been successful in the primary care setting. Methods. ED patients meeting National Institute on Alcohol Abuse and Alcoholism (NIAAA) criteria for at-risk drinking were recruited from 14 sites nationwide from April to August 2004. Control group patients received a written handout. Intervention group patients received the handout and participated in a 15 minute negotiated interview with direct referral for treatment if indicated. Among the 1,104 patients enrolled at baseline (538 intervention, 566 control), 63% completed follow-up surveys at three months by telephone Interactive Voice Response (IVR) system (n = 699). Results. At 3 months, patients receiving the intervention reported significantly lower levels of typical number of drinks per week' and 'maximum number of drinks per occasion,' controlling for baseline drinking levels: 3.25 fewer drinks per week than controls (B= -3.25 SE= 1.16, p < .05), and a level of maximum drinks per occasion of almost ¼ of a drink less than controls (B= -.72 SE= .32, p < .05). Benefits of brief intervention were confined to those with at-risk drinking rather than dependent drinking patterns, as measured by the CAGE.

Conclusions. This study demonstrates the effectiveness of SBIRT in the ED setting. Widespread use of SBIRT in EDs has the potential to significantly reduce rates of at-risk drinking, resulting in improvements to public health and significant health care cost savings.

SPID: 0557 **PROTOCOL:** 557 **TYPE:** RESEARCH

SHORT TITLE: Effects of DHEA and Exercise on Bone, Muscle and Balance

LONG TITLE: Effects of Dehydroepiandrosterone (DHEA) and Exercise on Bone, Muscle and Balance

AIDS:	N	TOTALS	A	B	D
		Inpatient	0	0	0
START DATE:	8/3/2004	Scatter Bed	0	0	0
Total # pts expected for entire study:	150	Outpatient	24	0	0
		Scatter RN Hours	0	0	0
		Offsite Visits	0	0	0

RESEARCH BIONUTRITION	N	MULTICENTER STUDY	N
INFORMATICS CORE	Y	CLINICAL TRIAL	N
BIostatistician	Y	CORE LAB	Y
ANCILLARIES ONLY	N		

INVESTIGATOR	DEPARTMENT	NON-HOST INSTITUTION: STATE, COUNTRY
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KENNY, ANNE M MD	CENTER ON AGING	
PRESTWOOD, KAREN MD	Medicine	

SUBPROJECT DESCRIPTION:

Bone and muscle loss in microgravity have been identified by National Aeronautics and Space Administration (NASA) as key barriers to successful long-term space flight. Further, the potential importance of balance effects of flight were highlighted by the disequilibrium findings in John Glenn following his return from a space shuttle flight and the initiative of NASA to assess longitudinally balance in cooperation with the Baltimore Longitudinal Aging Study. The bone and muscle loss in microgravity are not completely understood. There are several changes that occur during space travel that may influence changes in bone and muscle including weightlessness, hormone changes, nutritional changes, stress response, and protein metabolism (1, 2, 3). Many changes that occur with space travel are also seen with aging and culminate in a syndrome described as frailty (4,5,6). Changes with aging include increases in cortisol and insulin levels, decreases in sex hormones, poor nutritional intake and anorexia contributing to bone, muscle and balance loss. Study of interventions that may mitigate the effects of aging on frail, older individuals, may provide insights into countermeasures and strategies for minimizing bone, muscle and balance loss in space.

Most geriatricians agree that frailty is a syndrome of decreased reserve and resistance to stressors, resulting in cumulative declines across multiple physiologic systems, resulting in increased vulnerability to adverse outcomes (4,5,6). Physical markers of frailty include declines in lean body mass, strength, endurance, balance, walking performance, low activity and some include osteopenia (4,5,6,7). Many of the components of frailty are interrelated and all are associated with declining reserve. Since multiple of these components must be present clinically to constitute frailty, a physical continuum of robust to prefrail to frail can be envisioned. Fried et al. has proposed a phenotype of frailty, highlighting 5 characteristics from the physical markers of frailty, and used the phenotype to assess the contribution of baseline frailty status to the incidence of health outcomes during 3 and 7 years of follow-up (8). For this phenotype, frailty is defined as having 3 of the 5 characteristics and prefrailty has having 1 or 2 of the 5 characteristics. Frailty and prefrailty are associated with increased risk of death, hospitalization, falls, worsening Activities of Daily Living (ADL) disability and worsening mobility (8).

Dehydroepiandrosterone (DHEAS) and yoga may mitigate or reverse the effects of aging and frailty on bone, muscle and balance loss. The mechanism of the effects may be direct - working through androgen or estrogen receptors in bone, muscle or brain. Or the effects may be indirect, countering effects of the stress response.

Hypotheses: Muscle strength and balance will improve in women with frailty selected for dehydroepiandrosterone sulfate (DHEAS) levels below 305 ng/dl treated with DHEAS supplementation and Hatha yoga. The effects of both treatments will improve outcomes more than either treatment alone and may be additive. In addition, lean body mass, skeletal muscle mass, markers of bone turnover and physical performance will improve following treatment with DHEA and/or yoga.

SUBPROJECT PROGRESS:

The study is closed to recruitment and study visits were to complete classes and data collection by July 2006. There have been no safety concerns. There are no interim data or publications to date but we are currently working with statisticians to complete analysis and prepare manuscripts.

SPID: 0558 **PROTOCOL:** 558 **TYPE:** RESEARCH

SHORT TITLE: Clinical Behavior of Lithium Disilicate, Single-Unit, CAD/CAM Crowns

LONG TITLE: Clinical Behavior of Lithium Disilicate, Single-Unit, Computer-aided Design/Computer-aided Machining (CAD/CAM) Crowns

AIDS:	N	TOTALS	A	B	D
		Inpatient	0	0	0
START DATE:	8/5/2004	Scatter Bed	0	0	0
Total # pts expected for entire study:	40	Outpatient	25	0	0
		Scatter RN Hours	0	0	0
		Offsite Visits	0	0	0

RESEARCH BIONUTRITION	N	MULTICENTER STUDY	N	
INFORMATICS CORE	Y	CLINICAL TRIAL	Y	Phase III
BIostatistician	N	CORE LAB	N	
ANCILLARIES ONLY	N			

INVESTIGATOR	DEPARTMENT	NON-HOST INSTITUTION: STATE, COUNTRY
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KELLY, JOHN R DDS, DSC	Oral Rehab, Biomaterials	
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SQUIER, RACHEL DMD, DSC	Prosthodontics	
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SUBPROJECT DESCRIPTION:

This trial will examine the performance of 40 single unit crowns (25 posterior and 15 anterior) for a period of at least 2 years. Crowns will be fabricated from a lithium disilicate glass-ceramic using a computer-aided design/computer-aided machining (CAD/CAM) process. Both the material and the processing equipment have FDA 510-K clearance for this clinical application. The PI initiated this trial at UConn as an important complement to ongoing laboratory efforts to better understand clinical behavior and aid ongoing research into the development of validated laboratory tests of ceramic-ceramic compatibility and bulk fracture.

SUBPROJECT PROGRESS:

This study was closed to enrollment for the reporting period. All 1 year recall visits were completed and a few 2 year recalls finished. There were no additional bulk crown failures this year, no unexpected safety concerns and no changes to protocol. Final data analysis and reporting will not occur until after October 2007. Nothing related to this research has yet been published.

SPID:	0560	PROTOCOL:	560	TYPE:	RESEARCH	
SHORT TITLE:	Study of College Student Daily Life: Addendum - Interaction of Genetic					
LONG TITLE:	Study of College Student Daily Life: Addendum - Interaction of Genetic Variation and Daily Life Experiences					
AIDS:	N	TOTALS		A	B	D
		Inpatient		0	0	0
START DATE:	8/19/2004	Scatter Bed		0	0	0
Total # pts expected for entire study:	574	Outpatient		0	0	0
		Scatter RN Hours		0	0	0
		Offsite Visits		0	0	0
RESEARCH BIONUTRITION	N	MULTICENTER STUDY		N		
INFORMATICS CORE	N	CLINICAL TRIAL		N		
BIostatistician	N	CORE LAB		Y		
ANCILLARIES ONLY	N					

INVESTIGATOR	DEPARTMENT	NON-HOST INSTITUTION: STATE, COUNTRY
TENNEN, HOWARD PHD	Community Medicine	
AFFLECK, GLENN PHD	Community Medicine	
ARMELI, STEPHEN R PHD	PSYCHIATRY	FAIRLEIGH-DICKINSON UNIV, NJ USA
CILLESSEN, ANTONIUS PHD	PSYCHOLOGY	UConn, Storrs, CT USA
CONNER, TAMLIN PHD	Psychiatry	
COVAULT, JONATHAN MD, PHD	Psychiatry	
DEHART, TRACY PHD	PSYCHOLOGY	LOYOLA UNIV, IL USA
DUFFY, VALERIE PHD	ALLIED HEALTH SCIENCES	UConn, Storrs, CT USA
FORD, JULIAN D PHD	PSYCHIATRY	
GUNTHER, KATHLEEN PHD	PSYCHOLOGY	AMERICAN UNIVERSITY, DC USA
HERMAN, AREY BA	Psychiatry	
KRANZLER, HENRY R MD	PSYCHIATRY	

SUBPROJECT DESCRIPTION:

The proposed study is an addendum to an existing Alcohol Research Center longitudinal study of college students' daily alcohol consumption employing a daily report methodology to study the linkage of daily life events and students' health-related and school related behaviors. The 574 students currently enrolled in this study will be offered the opportunity to enroll in this genetics addendum which will (a) examine the influence of a functional polymorphism, 5-HTTLPR, in the promoter region of the serotonin transporter gene, and an alcohol dependence associated haplotype of the GABRA2 gene encoding the benzodiazapine receptor subunit GABRA a-2, on the use of alcohol by college students (b) evaluate the interaction of 5HTTLPR and GABRA2 genotypes with daily life stressors, positive experiences, social interactions/peer influences, and positive or negative mood states on the use of alcohol by college students. In an exploratory aim we will also examine the effects of variation in two other genes influencing serotonin signaling: i) Tph2 which encodes the brain specific form of tryptophan hydroxylase, the rate limiting enzyme in serotonin synthesis, and ii) MAOA encoding monoamine oxidase, a key enzyme involved in metabolic inactivation of synaptic serotonin (as well as norepinephrine and dopamine).

SUBPROJECT PROGRESS:

6 subjects enrolled in the genetics addendum portion of the study. For the entire study period 416 subjects enrolled. No changes in recruitment plans expected, 75% of eligible survey participants have enrolled. No further recruitment will occur. There have been no unexpected safety concerns. Examination of interim data show that the sample can be used to examine gene-environment interactions in relation to college student health related behaviors. The following findings listed in last year's report as being in press have now been published: Specifically, we found an interaction of past year life stress and a functional variant, 5-HTTLPR (5HT transporter gene-linked polymorphic region), of the serotonin transporter gene promoter such that subjects with low-activity promoter alleles were more likely to drink more frequently in proportion to their number of past year life stressors. Homozygous subjects without this low-activity promoter variant did not show a change in drinking behavior as a function of the number of stressful past year events. Refs: Covault, J., Tennen, H., Armeli, S., Conner, T., Herman, A., Cillesen, A.H.N., & Kranzler, H.R. (2007) Interactive effects of the serotonin transporter 5-HTTLPR polymorphism and stressful life events on college student drinking and drug use. Biol Psych, 61,

609-616. Another manuscript with additional findings is currently under review. Across the first two years of the study, diathesis-stress patterns were observed for reports of anxious mood as a function of 5-HTTLPR. Individuals with at least one copy of the S or LG allele of 5-HTTLPR experienced elevated anxious mood on days with more intense stressors, as compared with those who were LA homozygous. Genotype differences in anxiety were less apparent on low stress days. No consistent allelic association of 5-HTTLPR was observed with any of the other mood states, trait anxiety, or neuroticism

SPID: 0562	PROTOCOL: 562	TYPE: RESEARCH
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SHORT TITLE: Drug- and CAM-Induced Liver Injury

LONG TITLE: A Multi-Center, Longitudinal Study of Drug- and Complementary/Alternative Medicine (CAM)- Induced Liver Injury

AIDS:	N	TOTALS	A	B	D
			Inpatient	0	0
START DATE:	8/19/2004	Scatter Bed	0	0	0
Total # pts expected for entire study:	960	Outpatient	32	0	0
		Scatter RN Hours	0	0	0
		Offsite Visits	0	0	0

RESEARCH BIONUTRITION	N	MULTICENTER STUDY	Y
INFORMATICS CORE	Y	CLINICAL TRIAL	N
BIostatistician	N	CORE LAB	Y
ANCILLARIES ONLY	N		

INVESTIGATOR	DEPARTMENT	NON-HOST INSTITUTION: STATE, COUNTRY
BONKOVSKY, HERBERT L MD	MEDICINE/GASTROENTEROL OGY	
FRESTON, JAMES MD	Medicine	
ROSSON, ROBERT MD	Medicine	

SUBPROJECT DESCRIPTION:

Background and Rationale: Liver injury due to prescription and non-prescription medication use is a medical, scientific, and public health problem of increasing frequency and importance in the United States. Indeed, drug-induced liver injury (DILI) is the most common reason for nonapproval, withdrawal, limitation in use, and clinical monitoring by the Food and Drug Administration (FDA). However, detection of signals for liver injury frequently relies upon the reporting of cases by practitioners to health authorities in post-marketing surveillance. Under-reporting of cases, lack of mandatory reporting systems, and difficulties in establishing a diagnosis make the current system sub-optimal. Moreover, with the growing use of complementary and alternative medications (CAM), there have also been increasing reports of liver toxicity due to various non-prescription herbal, dietary, and food additive supplements. Because the manufacturing, dispensing, and testing of these products is not regulated, the hepatotoxic potential of these formulations is poorly characterized or completely unknown. As a result, there is a great need to develop an improved means of detecting, defining, and studying DILI in the United States.

The DILIN prospective study is a multi-center study designed to gather clinical information and biological specimens on cases of suspected liver injury due to drugs and CAM. The goals of this study include the earlier recognition of DILI, especially due to newer drugs, development of standardized instruments and terminology to help identify cases of DILI, investigating clinical and genetic risk factors that predict DILI, and performing a careful longitudinal follow-up of DILI subjects. The biological samples collected will be used in future studies of the mechanisms and genetics of DILI.

Specific Aims and Objectives: The primary objective of this study is to prospectively identify bona fide cases of liver injury due to drugs and complementary and alternative medications within 6 months of presentation. Secondary objectives include collecting clinical data and biological specimens including blood, DNA, urine, and liver tissue from affected patients and matched controls for future mechanistic and genetic studies. We will also investigate the clinical, immunological, and environmental risk factors of drug-mediated hepatotoxicity by comparing DILI cases to matched controls with a similar drug exposure history but no evidence of clinically significant liver injury. The natural history of drug- and CAM-induced DILI will be tracked for at least 6 months following enrollment, with longer follow-up for those in whom there is evidence of chronic liver injury at 6 months. We will also develop and test causality assessment instruments for drug and CAM-induced liver injury that are sensitive, specific, and reproducible.

Basic Study Design: The DILIN Prospective Study is a multi-center, prospective, epidemiological study. Patients who are referred to one of the DILIN clinical sites and who, in the opinion of a gastroenterologist / hepatologist, experienced a drug-induced liver injury will be enrolled. Detailed clinical data and biological specimens will be collected. Clinical data will be reviewed by the DILIN Causality Committee, and it will make the final determination of whether the subject qualifies as a bona fide DILI case. Up to three matched controls will be individually matched to each index case. They will be matched by age, duration of exposure to the

implicated medication, and from the same clinical site. DILI cases (only) will be followed for at least 6 months to derive the longitudinal profile of drug- and CAM-induced liver injury. Detailed clinical data and biological specimens will be collected at this time point. Patients who satisfy the definition of chronic DILI will be evaluated at 12 months and yearly thereafter.

SUBPROJECT PROGRESS:

A total of 49 subjects have consented to this study, 45 of whom were deemed eligible after the baseline visit. During the current reporting period, 25 eligible subjects have been enrolled. In our New England-Northeastern Consortium, we are establishing satellite sites to help identify and enroll suitable subjects throughout the northeastern quadrant of the USA. four sites have full approval: State University of New York (SUNY), Syracuse (PI: R. Levine); University of Rochester - Strong Memorial Hospital (PI: B. Maliakkal); Hartford Hospital (PI: R. Rosson); and Hebrew Health Care Inc. of Hartford. SUNY has screened 11 and enrolled 9 subjects, University of Rochester has screened 5 and enrolled 2 subjects. Hartford Hospital has screened 2 and referred 11 subjects 7 of which have been enrolled at UHC. Hebrew Health Care has screened 1 subject. Dartmouth-Hitchcock Medical Center (PI: D. van Leeuwen) has been a good source of subject referrals, 6 of whom have enrolled at UHC. There are no safety concerns to report. Because this is an observational study, primarily to develop a registry of subjects, there is minimal risk for subjects to take part, and we do not expect any significant adverse events. During the past year, the only modification submitted to the Institutional Review Board (IRB) was for approval of two registered letters to patients whom we were unable to contact by telephone. One letter is for patients who are potential subjects. The second letter is for patients who need to return for their six month visit. The Spanish version of the Hartford Hospital consent form was also submitted for approval.

SPID: 0563	PROTOCOL: 563	TYPE: RESEARCH
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SHORT TITLE: Substance Abuse Behavior

LONG TITLE: Individual Differences and Long-Term Follow-Up of Substance Use Behaviors

AIDS:		TOTALS	A	B	D
	N	Inpatient	0	0	0
START DATE:	9/16/2004	Scatter Bed	0	0	0
Total # pts expected for entire study:	210	Outpatient	20	0	0
		Scatter RN Hours	0	0	0
		Offsite Visits	0	0	0

RESEARCH BIONUTRITION	N	MULTICENTER STUDY	N
INFORMATICS CORE	Y	CLINICAL TRIAL	N
BIostatistician	N	CORE LAB	N
ANCILLARIES ONLY	N		

INVESTIGATOR	DEPARTMENT	NON-HOST INSTITUTION: STATE, COUNTRY
KING, ANDREA C PHD	DEPT OF PSYCHIATRY	UNIVERSITY OF CHICAGO, IL USA

SUBPROJECT DESCRIPTION:

The goal of this investigation is to compare unique behavioral and physiological responses to alcohol and their associations in light and heavy social alcohol drinkers. We plan to specify their objective, performance, and subjective alcohol response in a preclinical laboratory study. Measures will be obtained during both rising and declining blood alcohol concentrations in order to better understand potential factors involved in the earlier stages of heavy alcohol use. We also plan to follow-up on study participants for several years after the preclinical phase of the study to examine whether acute alcohol response factors are significantly associated with future drinking patterns and alcohol consequences.

SUBPROJECT PROGRESS:

For recruitment purposes, this protocol is commonly referred to as The Chicago Social Drinking Project (CSDP). Number of Enrolled Subjects: During the period of 4/1/06 3/31/07, the CSDP enrolled 19 subjects. During this period, we ceased enrollment, bringing our final total to 198 enrolled subjects. Of these 198 subjects, 190 completed all three required experimental sessions and are currently engaged in the longitudinal follow-up portion of the study. Changes in Recruitment Plan: The CSDP is no longer recruiting new subjects; thus, no changes in the recruitment plan are warranted. Unexpected Safety Concerns and Their Resolution: No unexpected safety concerns occurred during this reporting period. Interim Data and Outcome: During this period, the CSDP utilized the interactive voice recording (IVR) phone system provided by the University of Connecticut to complete quarterly follow-up data collection (at 3, 6, 9, 15, 18, and 21 months following the final in-lab experimental session). Data obtained from these follow-up interviews provide information regarding changes in the subject's alcohol consumption and cigarette smoking behavior as well as moods and significant life events. From 4/1/06 to 3/31/07, the CSDP successfully completed 453 of these phone interviews. Unsuccessfully completing only 4 interviews during this time period, the CSDP boasts an impressive 99.1% follow-up rate, thanks, in part, to the convenience of the IVR system. Proposed Changes to Protocol: No changes are proposed for this protocol. The publications did not include any information regarding longitudinal follow-up, and this protocol's involvement with the GCRC is only relevant to longitudinal follow-up, the GCRC was not cited in either publication.

SPID: 0566 **PROTOCOL:** 566 **TYPE:** RESEARCH

SHORT TITLE: PACTG P1057

LONG TITLE: Pediatric Clinical Trials Group (PACTG) P1057 (Version 1.0) - A Phase I/II Randomized Trial of the Safety and Immunogenicity of Cold Adapted Influenza Vaccine (Flumist) in HIV-Infected Children and Adolescents

AIDS:	Y	TOTALS	A	B	D
		Inpatient	0	0	0
START DATE:	10/1/2004	Scatter Bed	0	0	0
Total # pts expected for entire study:	20	Outpatient	0	0	0
		Scatter RN Hours	0	0	0
		Offsite Visits	0	0	0

RESEARCH BIONUTRITION	N	MULTICENTER STUDY	Y	
INFORMATICS CORE	Y	CLINICAL TRIAL	Y	Phase I-II
BIostatistician	N	CORE LAB	N	
ANCILLARIES ONLY	N			

INVESTIGATOR	DEPARTMENT	NON-HOST INSTITUTION: STATE, COUNTRY
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SALAZAR, JUAN C MD PEDIATRICS

SUBPROJECT DESCRIPTION:

The primary objectives of this study are: to compare the safety of FluMist with IAIV in Human Immunodeficiency Virus (HIV)-infected children and adolescents; to compare the immunogenicity of FluMist with IAIV in HIV-infected children and adolescents; and to determine prevalence and duration of viral shedding of FluMist in HIV-infected vaccines.

SUBPROJECT PROGRESS:

PACTG 1057 (Version 1.0) has had no enrollments during this report period. There have been 4 enrollments since the initiation of the protocol.

The protocol is currently closed to accrual, and the last patient visits have been conducted for this multi-centered trial. We are leaving it open in case of any data queries they may come up in the final analysis.

The team has not identified unanticipated concerns in its ongoing reviews of safety data that would warrant a change in the conduct of PACTG P1057.

There are no interim data or outcomes available. There are also no proposed or anticipated changes to the protocol.

SPID: 0567 **PROTOCOL:** 567 **TYPE:** RESEARCH

SHORT TITLE: PACTG P1051
LONG TITLE: Pediatrics Aids Clinical Trials Group (PACTG) P1051 A Multiple-Dose, Open-Label, Randomized, Safety and Pharmacokinetic Study of Tipranavir in Combination with Low Dose Ritonavir in HIV-Infected Pediatric Patients

AIDS:	Y	TOTALS	TOTALS		
			A	B	D
		Inpatient	0	0	0
START DATE:	8/1/2004	Scatter Bed	0	0	0
Total # pts expected for entire study:	20	Outpatient	0	0	0
		Scatter RN Hours	0	0	0
		Offsite Visits	0	0	0

RESEARCH BIONUTRITION	N	MULTICENTER STUDY	Y	
INFORMATICS CORE	Y	CLINICAL TRIAL	Y	Phase I-II
BIostatistician	N	CORE LAB	N	
ANCILLARIES ONLY	N			

INVESTIGATOR	DEPARTMENT	NON-HOST INSTITUTION: STATE, COUNTRY
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SALAZAR, JUAN C MD	PEDIATRICS	
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SUBPROJECT DESCRIPTION:

Assess the safety and tolerability of tipranavir (TPV) liquid formulation and soft elastic capsules with low-dose ritonavir in Human Immunodeficiency Virus (HIV)-infected children and adolescents, provide information concerning the pharmacokinetic characteristics of tipranavir in this age group, and determine the relative bioavailability of the TPV liquid formulation and TPV self-emulsifying drug delivery (SEDDS) capsule formulation in adolescents switching from liquid to capsule. A secondary objective of this study is the determination of the dose of TPV/r in children and adolescents between 2 and 18 years of age required for an adult equivalent systemic exposure of TPV/r 500 mg/200 mg.

SUBPROJECT PROGRESS:

No subjects were enrolled to PACTG 1051 (Version 10.14041) during the report period. There have been four enrollments since the initiation of this protocol.

There are no changes to the recruitment plans, as this study is closed to accrual.

The PACTG P1051 team regularly reviews safety data from this study. Based on cumulative data from April 2004 through September 2006, the protocol team has concluded that there are no safety concerns related to administration of tipranavir in the study population that would warrant a change in or cancellation of the study at this time. Data will continue to be evaluated periodically and sites will be notified of important safety information every six months as long as there continue to be subjects on study follow-up.

Change 1: All patients still active in the trial will be switched to the high dose, TPV 375 mg/m²+ RTV 150 mg/ m² b.i.d. Regardless of the new dose calculation, one single dose cannot exceed TPV 500 mg/RTV 200 mg, as already stipulated in the protocol. Patients who reach the 500 mg/200 mg threshold because of the dose increase can switch to TPV capsules. Based on the evaluation of the 48-week data for all 115 randomized patients, it appears that TPV/r high dose, TPV 375 mg/m²+RTV 150 mg/ m², is the appropriate dose for the pediatric population 2 to 18 years of age. Since patients still participating in this trial have been taking the TPV/r low dose since the interim analysis, all patients will need to be switched to the TPV/r high dose.

Change 2: Modification of Liver Function Testing management guidelines. Guidelines for management of increased ALT/AST are modified according to the new TPV project standard guidelines, which were based on careful analyses of the TPV safety database and are reflected in the current IB.

Change 3: Guidelines for management of cutaneous rash reactions are added to the protocol according to the new TPV project standard guidelines which were based on careful analyses of the TPV safety database and are reflected in the current IB.

Letter of Amendment #3 incorporates the following changes into the protocol:

Despite the release of BI Amendment #7, Change 2, IMPAACT-P1051 sites should continue to follow the guidelines for management

of LFT abnormalities currently included in Section 6.3.3.1, Selected Toxicity Management Guidelines of BI Revision D, 03 February 2005.

'b7 Patients with Grade 1 ALT or AST (1.1-4.9X ULN) will be continued on study treatment with routine monitoring.

'b7 Patients with Grade 2 ALT or AST (5.0-9.9X ULN) will be continued on study treatment with close monitoring. Other possible etiologies, eg., Hepatitis should be excluded and other concurrently collected clinical chemistries predictive of liver function should be reviewed.

'b7 Patients with Grade 3 ALT or AST (10.0-15Z ULN) will have all ARVs with held and LFTs rechecked in 1 week. IF AST of ALT has increased, discontinue from the study treatment. IF ALT or AST remains Grade 3 without increasing, recheck again in 1 week. If AST or ALT has decreased to Grade 2 or lower, TPV/r and all concomitant ARVs will be simultaneously reinitiated at the full dose. If the toxicity persist > 14 days or recurs after restarting TPV/r, discontinue TPV/r permanently.

'b7 Patients with Grade 4 ALT or AST (>15x ULN) will have all ARVs withheld and laboratory toxicities confirmed with repeat values obtained within 72 hours. If Grade 4 ALT or AST is confirmed, study treatment should be permanently discontinued and repeat laboratory values should be obtained at least weekly until the toxicity is <Grade 2.

Changes to the Consent

The new amendment has created changes to the sample informed consent; however, since this study is closed to enrollment and all subjects at this site have finished the study, we are not submitting a consent form for approval, as one done at the last continuation.

SPID: 0568 **PROTOCOL:** 568 **TYPE:** RESEARCH

SHORT TITLE: Chemotherapy Induced Thrombophilia

LONG TITLE: Chemotherapy Induced Thrombophilia

AIDS:	N	TOTALS	A	B	D
		Inpatient	0	0	0
START DATE:	10/19/2004	Scatter Bed	0	0	0
Total # pts expected for entire study:	10	Outpatient	0	0	0
		Scatter RN Hours	0	0	0
		Offsite Visits	0	0	0

RESEARCH BIONUTRITION	N	MULTICENTER STUDY	N
INFORMATICS CORE	Y	CLINICAL TRIAL	N
BIostatistician	N	CORE LAB	Y
ANCILLARIES ONLY	N		

INVESTIGATOR	DEPARTMENT	NON-HOST INSTITUTION: STATE, COUNTRY
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BONA, ROBERT MD	Medicine/Hem-Onc	
HEGDE, UPENDRA MD	Medicine	
HLA, TIMOTHY T PHD	CELL BIOLOGY	
SMARADOTTIR, AGNES MD	Medicine/Hem-Onc	

SUBPROJECT DESCRIPTION:

The hypothesis for this study is that chemotherapy itself induces thrombophilic state in cancer patients by causing endothelial damage and therefore is able to activate the coagulation system. It is our aim to show that markers of endothelial damage and activation of the coagulation cascade is induced when patients receive chemotherapy. Each patient will serve as his/her own control.

SUBPROJECT PROGRESS:

Accrual to the study has been closed. Most laboratory analysis has been completed (the labs performed by the GCRC lab have all been completed) There have been no unexpected safety concerns.

SPID: 0569 **PROTOCOL:** 569 **TYPE:** RESEARCH

SHORT TITLE: Breaking the Cycle of Behavioral Health Problems

LONG TITLE: Breaking the Cycle of Behavioral Health Problems

AIDS:	N	TOTALS	A	B	D
		Inpatient	0	0	0
START DATE:	7/1/2004	Scatter Bed	0	0	0
Total # pts expected for entire study:	135	Outpatient	0	0	0
		Scatter RN Hours	0	0	0
		Offsite Visits	0	0	0

RESEARCH BIONUTRITION	N	MULTICENTER STUDY	N
INFORMATICS CORE	Y	CLINICAL TRIAL	N
BIostatistician	N	CORE LAB	N
ANCILLARIES ONLY	N		

INVESTIGATOR	DEPARTMENT	NON-HOST INSTITUTION: STATE, COUNTRY
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FORD, JULIAN D PHD	PSYCHIATRY	
ABU-HASABALLAH, KHAMIS PHD	Psychiatry	
ALBERT, DAVID PHD	Psychiatry	
MOFFITT, KATHIE H PHD	Psychiatry	
STEINBERG, KAREN L PHD	PSYCHIATRY	
TANEV, KALOYAN MD	Psychiatry	
TENNEN, HOWARD PHD	Community Medicine	

SUBPROJECT DESCRIPTION:

The study is comparing two psychotherapy interventions with an active comparison condition to determine their efficacy in addressing behavioral, cognitive, affective, and interpersonal substrates of a core problem in complex Post Traumatic Stress Disorder (PTSD) that often occurs for persons living in adverse socioeconomic circumstances and in violent families and communities. One goal of the study is to reduce the severity of or produce remission from PTSD and associated anxiety, mood, and addictive disorders, in order to reduce impulsivity, aggression, dissociation, and isolation by high-risk or previously incarcerated women. The long-term goal, which will be assessed in subsequent studies over time is to reduce the likelihood of their or their children becoming involved in, or victimized by other persons' involvement in, illegal activities. Children will not be involved in the present study, only women who are the mothers of young children.

Aim #1: To test the efficacy of TARGET and PCT. TARGET (Frisman, Ford, & Lin, 2004) and PCT (McDonagh-Coyle, Friedman, McHugo, Ford et al., in press) have demonstrated efficacy in randomized trial studies, but have not been tested specifically with mothers of young children. The study will assess outcomes that are of potential importance not only for the well being of the participating women but for their ability to develop secure attachments with their child which are protective against exposure to violence, crime, and victimization and associated with positive psychosocial development by children. Outcome measures reflect self-regulatory capacities compromised by trauma which are essential for effective caregiving by adults.

Aim #2: To compare the efficacy of TARGET and PCT on theory-based differential outcomes. TARGET and PCT use similar but different therapeutic strategies. Each teaches skills for managing negative emotions and critical symptoms (e.g., inhibiting impulsivity). TARGET teaches a skill sequence for affect regulation and social/interoceptive information processing, while PCT teaches a skill sequence for recognizing and solving problems in relationships. We expect that TARGET and PCT will reduce stress-related avoidance and depression and enhance active coping with current stressors. TARGET should be superior to PCT in enhancing the ability to cope with trauma memories, stress reactivity, and anxiety, and therefore, physical well-being and ability to remain free from illegal activities or future or further involvement with criminal justice systems. PCT should be superior to TARGET in enhancing the participant's overall social adjustment.

SUBPROJECT PROGRESS:

Number of subjects enrolling during the report period and since initiation of the study During report period: 75 Since initiation of the study: 174 Any changes in recruitment plans that might be needed N/A - the study is currently closed to recruitment. Unexpected safety concerns and their resolution None Interim data and outcomes if appropriate None available Any proposed changes made or

anticipated in the protocol None anticipated. Publications, indicating whether the GCRC was cited None at this time.

SPID: 0570	PROTOCOL: 570	TYPE: RESEARCH
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SHORT TITLE: Pompe Registry

LONG TITLE: Pompe Registry

AIDS:		TOTALS	A	B	D
	N	Inpatient	0	0	0
START DATE:	11/18/2004	Scatter Bed	0	0	0
Total # pts expected for entire study:	10	Outpatient	0	0	0
		Scatter RN Hours	0	0	0
		Offsite Visits	0	0	0

RESEARCH BIONUTRITION	N	MULTICENTER STUDY	Y
INFORMATICS CORE	Y	CLINICAL TRIAL	N
BIostatistician	Y	CORE LAB	N
ANCILLARIES ONLY	N		

INVESTIGATOR	DEPARTMENT	NON-HOST INSTITUTION: STATE, COUNTRY
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WHITAKER, CHARLES MD	Medicine/Neurology	
FELICE, KEVIN DO	Medicine/Neurology	
GREENSTEIN, ROBERT MD	Pediatrics/Genetics	

SUBPROJECT DESCRIPTION:

The primary objectives of the Pompe Registry are:

- To enhance the understanding of the variability, progression, and natural history of the key manifestations of Pompe disease
- To assist the Pompe medical community with the development of recommendations for monitoring patients and reports on patient outcomes to help optimize patient care; and
- To characterize and describe the Pompe disease population as a whole.

SUBPROJECT PROGRESS:

During the current report period of 4/1/06 to 3/31/07, no new subjects have been enrolled in this study. Since initiation of this registry there has been a total of 1 subject enrolled. The FDA recently approved a drug for the treatment of Pompe. It is our hope that this will help identify and enroll more patients in this registry. There were no unexpected safety concerns for this report period. No changes have been made to the protocol and ICF at this time nor are there anticipated changes to the protocol. There is no interim data and outcomes to report. There are no publications for this study.

SPID:	0572	PROTOCOL:	572	TYPE:	RESEARCH	
SHORT TITLE:	Oral Infection and Inflammation in Transplant Patients					
LONG TITLE:	Oral Infection and Inflammation in Transplant Patients					
AIDS:	N	TOTALS		A	B	D
		Inpatient		0	0	0
START DATE:	9/30/2004	Scatter Bed		0	0	0
Total # pts expected for entire study:	108	Outpatient		131	0	0
		Scatter RN Hours		0	0	0
		Offsite Visits		0	0	0
RESEARCH BIONUTRITION	N	MULTICENTER STUDY		Y		
INFORMATICS CORE	Y	CLINICAL TRIAL		N		
BIostatistician	N	CORE LAB		Y		
ANCILLARIES ONLY	N					

INVESTIGATOR	DEPARTMENT	NON-HOST INSTITUTION: STATE, COUNTRY
DONGARI-BAGTZOGLU, ANNA I DDS, PHD	PERIODONTOLOGY	
BURLESON, JOSEPH PHD	Behavioral Sciences	
HULL, DAVID MD	SURGERY	HARTFORD HOSPITAL, CT USA
IOANNIDOU, EFFIE DDS	Periodontology	

SUBPROJECT DESCRIPTION:

Chronic periodontitis and oral candidiasis are the most frequent opportunistic oral infections associated with immunosuppression caused by disease or treatment. These oral infections are frequently asymptomatic and therefore can remain undiagnosed and untreated. Solid organ transplant recipients represent a growing population of chronically immunosuppressed patients whose oral health status has been largely uncharacterized. Because recent studies have shown that chronic oral infection can trigger low grade systemic inflammation which may contribute to vascular disease and because chronic graft vasculitis can lead to transplant rejection, studies characterizing the oral and systemic inflammatory status in this patient population are urgently needed. Serum interleukin-6 (IL-6) and C-reactive protein (CRP) are well established, sensitive markers of systemic inflammation which have been shown to be elevated in chronic periodontitis patients and are also good diagnostic indicators for transplant rejection. In this proposal we hypothesize that in transplant patients with Candida stomatitis or chronic periodontitis, chronic elevation of serum IL-6 may directly or indirectly (via induction of CRP) be associated with chronic graft allograft failure.

To begin to explore a potential relationship between chronic oral opportunistic infection and chronic transplant rejection we propose to a) study the prevalence of oral candidiasis and chronic periodontitis in their patients population; b) collect preliminary data on a possible association between the presence of these oral opportunistic infections and a history of chronic rejection; and c) determine the levels of IL-6 and CRP in the serum of transplant patients and study their relationship with i) the presence of oral infection; and ii) the levels of oral mucosal IL-6 expression in situ. The pilot work proposed herein will provide the framework for the design of a larger scale prospective clinical study which will conclusively address the role of oral opportunistic infections in systemic inflammation and chronic transplant rejection in this special needs patient population.

SUBPROJECT PROGRESS:

We have enrolled more than 115 transplant patients at Hartford Hospital and more than 70 healthy subjects at UCHC since initiation of the study (approximately 40 subjects last year). This study is now closed to recruitment. There were no unexpected concerns or changes in plans/protocol. One paper has been published and the GCRC was cited. Elevated serum IL-6 in solid organ transplant recipients is positively associated with tissue destruction and IL-6 gene expression in the periodontium, by Ioannidou E et al (J Periodontol, 77: 1871-1878, 2006. This report shows a positive association between oral and systemic inflammation levels in solid organ transplant recipients. The following abstracts were accepted for presentation: 1. Dongari-Bagtzoglou AI, Ioannidou E*, Dwivedi P*, Burleson J, Hull D. Oral Candida colonization in solid organ transplant recipients. Presented, 14th International Symposium of Infections in the Immunocompromised Host, 2006, Crans Montana, Switzerland. 2. Kao D*, Ioannidou* E, Chang N*, Dongari-Bagtzoglou AI. Serum IL-6 in solid organ transplant recipients is positively associated with tissue destruction and IL-6 gene expression in the periodontium. Orban Competition Finalist, Presented, 2006 AAP Meeting, San Diego, CA. 3. Ioannidou E*, Kao D*, Chang N*, Hull D, Burleson J, Dongari-Bagtzoglou AI. Periodontal and systemic inflammation in transplant subjects". Presented,

2006 AADR meeting, Orlando, FL. 4. Kao D*, Ioannidou* E, Chang N*, Dongari-Bagtzoglou AI. "Oral colonization of transplant subjects with *Candida albicans*" Presented, 2006 AADR meeting, Orlando, FL.

SPID: 0574 **PROTOCOL:** 574 **TYPE:** RESEARCH

SHORT TITLE: CO2 Production and Ventilation in COPD

LONG TITLE: CO2 Production and Ventilation in Chronic Obstructive Pulmonary Disease (COPD)

	AIDS:	N	TOTALS			
				A	B	D
			Inpatient	0	0	0
START DATE:		5/19/2005	Scatter Bed	0	0	0
Total # pts expected for entire study:		50	Outpatient	5	0	0
			Scatter RN Hours	0	0	0
			Offsite Visits	0	0	0

RESEARCH BIONUTRITION	N	MULTICENTER STUDY	N
INFORMATICS CORE	N	CLINICAL TRIAL	N
BIostatistician	N	CORE LAB	N
ANCILLARIES ONLY	N		

INVESTIGATOR	DEPARTMENT	NON-HOST INSTITUTION: STATE, COUNTRY
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BURKI, NAUSHERWAN K MD	Medicine/Pulmonary Medicin	
MARTIN, ISHMAEL MD	Pulmonary	
SALERMO, EDWARD MD	Medicine/Pulmonary	

SUBPROJECT DESCRIPTION:

1. Resting minute ventilation (V_e) is increased in normocapnic patients with COPD.
2. The ratio of CO₂ production (V_{CO_2}) to resting V_e , is decreased in COPD
3. Whilst the relationship V_{CO_2} /arterial PCO₂ in COPD is similar to normals, the relationship V_e /arterial PCO₂ is decreased.
4. V_{CO_2} is similar in normocapnic and hypercapnic COPD, but V_e/V_{CO_2} is decreased in hypercapnic vs normocapnic COPD.
5. In contrast to normal subjects, both normocapnic and hypercapnic COPD patients respond to an added respiratory resistive load with a decrease in V_e and increase in end-tidal PCO₂.

SPECIFIC AIMS

1. In patients with normocapnic COPD, and in healthy normal subjects, measure resting V_e , V_{CO_2} , end-tidal CO₂ and anatomic deadspace (V_{dan}) and alveolar deadspace (V_{dalv}) and examine the relationship amongst these parameters and in relationship to arterial PCO₂ (PaCO₂).
2. In patients with hypercapnic COPD, measure resting V_e , V_{CO_2} , end-tidal CO₂, PaCO₂, V_{dan} and V_{dalv} and examine the relationship amongst these parameters, and compare the results to normocapnic COPD patients.
3. In normocapnic and hypercapnic COPD patients, and in healthy normal subjects, examine the effects of an added resistive load on V_e , V_{CO_2} , and end-tidal CO₂ to approximate the effects of acute exacerbations of COPD on these parameters. Ventilatory failure is associated with an increased arterial PCO₂ (PaCO₂). Arterial PaCO₂ is determined by the balance between CO₂ production and excretion from the body (V_{CO_2}). CO₂ production is known to be increased in obesity (1), during exercise (2), fever, and with high carbohydrate diets (3, 4).

The critical importance of CO₂ has been recognized for a very long time: Were it not for the peculiar properties of carbon dioxide - a very weak acid and a gas - our bodies would be unable to survive in their present state" (5). A great deal is known about the production of CO₂ (V_{CO_2}) by the human body as a natural physiologic process: CO₂ is produced in muscle as a product of metabolism, diffuses rapidly into blood where it is transported to the lungs and excreted.

The production of CO₂ is dependent on three factors: metabolism, blood carriage mechanisms (acid/base, buffering mechanisms), and pulmonary excretion.

Dietary factors which alter CO₂ production are due to the differences between carbohydrates and fat: in glycolysis, 1 mol of CO₂ is produced in regenerating 6 mol of ATP, whereas in non-esterified fatty acid metabolism 1 mol of CO₂ is produced for 8 mol of ATP. Thus CO₂ production is dependent on the balance between fat and glycogen oxidation, and can be influenced by dietary changes (3, 4).

CO₂ is carried in the blood as dissolved CO₂ and [HCO₃⁻] and is affected by the acid -base state. The excretion of CO₂ by the

lungs is considered primarily a function of ventilation, and complete equilibration is assumed between the PCO₂ of capillary blood and the alveoli (2). However, under stress, such as during exercise, a disequilibrium occurs, related to the breathing cycle and blood flow. In healthy normal subjects there is a direct, curvilinear relationship between alveolar ventilation (VA) and arterial PCO₂.

SUBPROJECT PROGRESS:

A total of 38 subjects have been studied, including COPD patients and Normal subjects. Valid data were available in 26 COPD patients (15 females, mean age 67±10yrs), including 11 patients with resting hypercapnia, and 9 normal subjects (4 females; age 33.1±9.6yrs). The data indicate that 1. Compared to normal subjects, resting minute ventilation is increased in normocapnic COPD patients, but not in hypercapnic COPD patients. 2. O₂ uptake (VO₂) is not significantly altered in COPD patients compared to normal subjects, even in the presence of increased airways resistance. 3. There is a tendency to increased CO₂ production in hypercapnic COPD patients, although the difference from normal subjects was not significant. 4. However, VCO₂/V_e, an index of the efficiency of CO₂ removal, is significantly reduced in normocapnic COPD patients, but not in hypercapnic patients. 5. There is a significant negative correlation between VCO₂/V_e and V_d/V_t and, surprisingly, a significant positive correlation with PaCO₂. 6. These findings may be due to fact that with the development of hypercapnia, the correlation between minute ventilation and V_d/V_t is lost. There are no planned changes in recruitment, and there have been no safety concerns.

SPID: 0575	PROTOCOL: 575	TYPE: RESEARCH
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SHORT TITLE:	NSABP B39
LONG TITLE:	NSABP B39/RTOG 0413: A Randomized Phase III Study of Conventional Whole Breast Irradiation (WBI) Versus Partial Breast Irradiation (PBI) for Women with Stage 0, I, or II Breast Cancer

	AIDS:	N	TOTALS	A	B	D
			Inpatient	0	0	0
START DATE:		4/28/2005	Scatter Bed	0	0	0
Total # pts expected for entire study:		10	Outpatient	0	0	0
			Scatter RN Hours	0	0	0
			Offsite Visits	0	0	0

RESEARCH BIONUTRITION	N	MULTICENTER STUDY	Y
INFORMATICS CORE	Y	CLINICAL TRIAL	N
BIostatistician	N	CORE LAB	N
ANCILLARIES ONLY	N		

INVESTIGATOR	DEPARTMENT	NON-HOST INSTITUTION: STATE, COUNTRY
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KURTZMAN, SCOTT MD	Surgery	
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SUBPROJECT DESCRIPTION:

Breast conserving therapy (BCT) has become an accepted option in the treatment of most patients with Stage 1 and 2 breast cancer. The major advantages of BCT are superior cosmetic results and reduced psychological and emotional trauma compared to mastectomy. However, BCT also has disadvantages. The technique is more complex and prolonged treatment regimen requiring approximately 5-7 weeks to complete. For patients who are elderly or whom live a distance from treatment centers, logistical problems can prove to be prohibitive. In addition, with the more frequent use of adjuvant chemotherapy in patients with both node negative and node positive breast cancer, delays can occur prior to the initiation of radiation therapy or hormonal therapy. Despite the advantages of BCT, only 10-40% of patients who are candidates for BCT actually receive it. Most of the logistical problems associated with BCT relate to the protracted course of external beam radiation to the whole breast. Standard therapy generally includes 5 weeks of radiation to the whole breast followed by a boost to the tumor bed with either additional 8-10 fractions of external beam radiation or 2-3 day interstitial implant. Studies have shown that it appears radiation therapy after tumor excision exerts its maximal effect upon reducing breast cancer recurrence at or near the tumor site.

The primary aim of the study is to determine whether partial breast irradiation (PBI) limited to the region of the tumor bed following lumpectomy provides equivalent local tumor control in the breast compared to conventional whole breast irradiation (WBI) in the local management of early stage breast cancer. The secondary aims are 1) to compare overall survival, recurrence-free survival, and distance disease-free survival between women receiving PBI vs. WBI; 2) to determine whether PBI delivered on 5 treatment days over a period of 5-10 days can provide a comparable cosmetic result to WBI; 3) to determine if PBI produces less fatigue and treatment-related symptoms compared to WBI; 4) to determine if perceived convenience of care is greater for women receiving PBI compared to women receiving WBI; and 5) to compare acute and late toxicities between the radiation therapy regimens.

SUBPROJECT PROGRESS:

We have not enrolled any patients onto this study. There will be no changes made to the recruitment. At this time there are no unexpected safety concerns and no anticipated changes to the protocol. There are no publications that cite the GCRC.

SPID: 0576	PROTOCOL: 576	TYPE: RESEARCH
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SHORT TITLE:	NSABP R04
LONG TITLE:	NSABP R04: Treatment with Two Chemotherapy Drugs Combined with Radiation Therapy for Patients with Rectal Cancer

	AIDS:	N	TOTALS			
				A	B	D
			Inpatient	0	0	0
START DATE:		4/28/2005	Scatter Bed	0	0	0
Total # pts expected for entire study:		10	Outpatient	0	0	0
			Scatter RN Hours	0	0	0
			Offsite Visits	0	0	0

RESEARCH BIONUTRITION	N	MULTICENTER STUDY	Y
INFORMATICS CORE	Y	CLINICAL TRIAL	N
BIostatistician	N	CORE LAB	N
ANCILLARIES ONLY	N		

INVESTIGATOR	DEPARTMENT	NON-HOST INSTITUTION: STATE, COUNTRY
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KURTZMAN, SCOTT MD	Surgery	
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SUBPROJECT DESCRIPTION:

Rectal cancer remains a significant oncologic problem, with approximately 34,700 new cases diagnosed each year with an expected overall 5-year survival of 50%. Surgical resection is the primary therapy, which unfortunately often requires creation of permanent colostomy. Due to high recurrence rate with surgery alone, adjuvant chemoradiation has become standard practice for the treatment of advanced rectal cancer. However, the optimal treatment schedule remains unknown. This protocol will examine if preoperative radiotherapy plus capecitabine is similar to preoperative radiotherapy (XRT) plus continuous intravenous infusion (CVI) of 5-FU in achieving durable local-regional disease control. Because studies using postoperative chemotherapy and radiotherapy did not improve disease free survival or overall survival, more recent trials have been looking at preoperative radiotherapy. A trial conducted in Sweden, using preoperative radiotherapy reports a significant increase in survival and similar trials conducted by the Dutch has shown a decrease in local recurrence. The clinical usefulness of capecitabine has been demonstrated in 2 large phase 3 studies comparing 5-FU to capecitabine in untreated colorectal patients. The studies have shown that oral administration of capecitabine results in higher response rate than 5-FU. Also, capecitabine has certain characteristics that make it a potentially useful radiosensitizer. The primary aim is to compare the rate of local-regional relapse in patients receiving preoperative oral capecitabine with XRT to CVI 5-FU and XRT. The secondary aims are to downstage the primary tumor, increase the number of patients undergoing sphincter-saving surgery, correlate genetic patterns and the presence of absence of specific tissue biomarkers with response and prognosis, compare capecitabine and CVI 5-FU in the setting of preoperative XRT for rectal cancer, examine the differences in toxicity and burden of care for the 2 chemotherapy treatment regimens, and to describe the impact of the type of surgical management of rectal cancer on QOL at 1 year after surgical treatment.

Study Design

Patients must have histologically diagnosed adenocarcinoma of the rectum, be amenable to surgical resection and tumor must be located < 12cm from the anal verge. Patients will then be stratified by gender, tumor stage, and intent for surgery. Following stratification they are randomized to receive either CVI 5-FU and XRT or capecitabine and XRT. The chemotherapy ends with the last XRT dose. This is followed by surgery.

SUBPROJECT PROGRESS:

We have not enrolled any patients on this study and there will be no changes made to the recruitment plans. There are no unexpected safety concerns and no anticipated changes to the protocol. The GCRC is not cited in any publications.

SPID: 0577	PROTOCOL: 577	TYPE: RESEARCH
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SHORT TITLE: NSABP B-38

LONG TITLE: NSABP B38: A Phase III, Adjuvant Trial Comparing Three Chemotherapy Regimens in Women with Node-Positive Breast Cancer

AIDS:	N	TOTALS	A	B	D
			Inpatient	0	0
START DATE: 4/28/2005		Scatter Bed	0	0	0
Total # pts expected for entire study:	10	Outpatient	0	8	0
		Scatter RN Hours	0	0	0
		Offsite Visits	0	2	0

RESEARCH BIONUTRITION	N	MULTICENTER STUDY	Y	
INFORMATICS CORE	Y	CLINICAL TRIAL	Y	Phase III
BIostatistician	N	CORE LAB	N	
ANCILLARIES ONLY	N			

INVESTIGATOR	DEPARTMENT	NON-HOST INSTITUTION: STATE, COUNTRY
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KURTZMAN, SCOTT MD	Surgery	
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SUBPROJECT DESCRIPTION:

Recently, oncologists have begun treating breast cancer patients with dose dense (DD) regimens. This means that the patients receive the chemotherapy drugs over a much shorter period of time. Surprisingly, the overall toxicities experienced by the patients is no worse and the efficacy equal if not superior. Studies have shown that women with breast cancer treated with Docetaxel/Doxorubicin/Cyclophosphamide (TAC) (Arm I) or ddose-dense. Doxorubicin/Cyclophosphamide followed by DD Paclitaxel (DD AC-P) (Arm II) have improved treatment outcome compared to previously used chemotherapy regimens. Unfortunately some women still develop local, regional, and systemic disease recurrence. This reality provides a compelling reason to continue efforts to further improve therapy for node-positive breast cancer. To date there has not been a study to directly compare TAC to DD AC-P and this trial will provide that comparison. Another potential advantage of DD AC-P is that it's reported toxicity profile provides opportunity for incorporating a fourth chemotherapy agent into the program. The anti-metabolite gemcitabine has shown promise in combination with paclitaxel for treatment of metastatic breast cancer arguing for its potential use in the adjuvant setting. A phase 2 study of gemcitabine in combination with paclitaxel as a third-line therapy showed a response rate of 55% with a manageable toxicity profile. On the basis of the activity of the gemcitabine/paclitaxel combination demonstrated in these trials, coupled with the favorable toxicity profile of the dose-dense schedule, they propose to determine whether sequential dose-dense AC followed by DD AC-PG (Arm III) can further improve the outcome provided by both TAC and DD AC-P.

The primary aims of this study are to determine whether the DD AC-PG regimen is superior to the TAC and the DD AC-P regimens in improving DFS and to compare the relative DFS of TAC and DD AC-P. Secondary aims are to determine whether DD AC-PG is superior to TAC and DD AC-P in improving overall survival, compare survival of the TAC and DD AC-P regimens Alone, and to compare the toxicities of the 3 regimens.

Study Design: The study will be conducted in women with operable, invasive carcinoma of the breast with histologically positive axillary nodes. Patients will be stratified by number of positive nodes, hormone receptor status, and type of surgery and planned radiotherapy. Following stratification, patients will be randomized to 1 of the 3 chemotherapy regimens. Women with ER positive and/or PR positive tumors should receive hormonal therapy for a minimum of 5 years following completion of chemotherapy. All women who have had a lumpectomy will have whole breast irradiation. Chest wall and regional nodal irradiation will be prospectively determined at the discretion of the investigator and will be used as a stratification factor. The study will enroll 4800 patients.

SUBPROJECT PROGRESS:

We have 8 patients currently on study. Eight patients have completed their study treatment and are in the follow-up phase and doing well. There are no changes in the recruitment plans. No anticipated changes to the protocol. There are no publications citing the GCRC.

SPID: 0578 **PROTOCOL:** 578 **TYPE:** RESEARCH

SHORT TITLE: NSABP B36

LONG TITLE: NSABP B36: A Clinical Trial of Adjuvant Therapy Comparing 6 Cycles of 5-FU, Epirubicin and Cyclophosphamide (FEC) to 4 Cycles of Adriamycin and Cyclophosphamide (AC), With or Without Celecoxib, in Patients with Node Negative Breast Cancer

AIDS:	N	TOTALS	A	B	D
		Inpatient	0	0	0
START DATE:	4/28/2005	Scatter Bed	0	0	0
Total # pts expected for entire study:	50	Outpatient	0	0	0
		Scatter RN Hours	0	0	0
		Offsite Visits	0	0	0

RESEARCH BIONUTRITION	N	MULTICENTER STUDY	Y	
INFORMATICS CORE	Y	CLINICAL TRIAL	Y	Phase III
BIostatistician	N	CORE LAB	N	
ANCILLARIES ONLY	N			

INVESTIGATOR	DEPARTMENT	NON-HOST INSTITUTION: STATE, COUNTRY
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KURTZMAN, SCOTT MD	Surgery	
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SUBPROJECT DESCRIPTION:

The primary aim of this phase III trial are to determine whether a regimen of 6 cycles of 5-fluorouracil (5-FU), epirubicin and cyclophosphamide (FEC-100) is superior to 4 cycles of Adriamycin and cyclophosphamide (AC) in prolonging disease-free survival (DFS) in patients with node-negative breast cancer. Chemotherapy (AC or FEC-100) plus celecoxib is superior to chemotherapy along in prolonging DFS in women with node-negative breast cancer.

SUBPROJECT PROGRESS:

We have not enrolled any patients into this study. There is no recruitment plan in place except for capturing potential patients during the breast cancer multi-disciplinary meetings. No unexpected safety concerns. There are no anticipated changes forthcoming. No publications citing the GCRC.

SPID: 0579 **PROTOCOL:** 579 **TYPE:** RESEARCH

SHORT TITLE: NSABP C08
LONG TITLE: NSABP C08: A Phase III Clinical Trial Comparing Infusional 5-Fluorouracil (5-FU), Leucovorin and Oxaliplatin (mFOLFOX6) Every Two Weeks With Bevacizumab to the Same Regimen Without Bevacizumab for the Treatment of Patients with Resected Stages II an

AIDS:	N	TOTALS	A	B	D
			Inpatient	0	0
START DATE:	4/28/2005	Scatter Bed	0	0	0
			Total # pts expected for entire study:	10	Outpatient
		Scatter RN Hours	0	0	0
		Offsite Visits	0	0	0

RESEARCH BIONUTRITION	N	MULTICENTER STUDY	Y	
INFORMATICS CORE	Y	CLINICAL TRIAL	Y	Phase III
BIostatistician	N	CORE LAB	N	
ANCILLARIES ONLY	N			

INVESTIGATOR	DEPARTMENT	NON-HOST INSTITUTION: STATE, COUNTRY
KURTZMAN, SCOTT MD	Surgery	
DECKERS, PETER MD	Surgery	
HEGDE, UPENDRA MD	Medicine	
TANNENBAUM, SUSAN MD	Medicine/Hem-Onc	
ZARFOS, KRISTEN MD	Surgery	

SUBPROJECT DESCRIPTION:

Colorectal cancer is the third most common cause of death from malignancy in both males and females in the U.S. Although surgery remains the mainstay of treatment for stages II and III colon cancer, a substantial minority of patients are not cured by surgery along. Studies have shown that adding adjuvant chemotherapy, 5-FU and leucovorin (LV) have increased disease free survival (DFS) and survival (S) rates, which has become current standard of care. Recently studies have shown that by adding oxaliplatin the DFS rate was significantly improved. Studies conducted with bevacizumab (antiangiogenesis agent) in patients with advanced colorectal cancer have shown tangible benefit to adding bevacizumab to the chemotherapy. The Federal Drug Administration approved the use of bevacizumab in combination with 5-FU and leucovorin as first line of treatment for patients with advanced colorectal cancer. The hypothesis of this trial is that the addition of bevacizumab (anti-VEGF antibody) to infusional 5-FU + LV and oxaliplatin will be more beneficial than oxaliplatin alone in prolonging DFS and S in patients with resected stages 2 and 3 carcinoma of the colon.

Treatment Plan: Patients in Group 1 will receive oxaliplatin 85mg/m² with concurrent LV 400 mg/m² on Day 1 of each 2-week cycle followed by IV bolus 5-FU 400 mg/m² followed by a single continuous infusion of 5-FU 2400 mg/m² over 46 hours. This treatment regimen will be repeated every 2 weeks for a total of 12 cycles (6 months). Patients in Group 2 will receive oxaliplatin 85 mg/m² with concurrent LV 400 mg/m² on Day 1 of each 2 week cycle followed by IV bolus 5-FU 400 mg/m² followed by a single continuous infusion of 5-FU 2400 mg/m² over 46 hours. This treatment regimen will be repeated every 2 weeks for a total of 12 cycles (6 months). Bevacizumab 5 mg/kg IV will be administered before oxaliplatin on Day 1 of each chemotherapy cycle and continue ever 2 weeks during and after the completion of all chemotherapy cycles for a total duration of 1 year.

SUBPROJECT PROGRESS:

This study has been terminated. No patients enrolled.

SPID: 0581	PROTOCOL: 581	TYPE: RESEARCH
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SHORT TITLE: Changing ART Adherence Behavior

LONG TITLE: Changing Antiretroviral (ART) Adherence Behavior for HIV-related Morbidity and Mortality

AIDS:	Y	TOTALS	A	B	D	
			Inpatient	0	0	0
START DATE: 4/28/2005			Scatter Bed	0	0	0
			Total # pts expected for entire study: 360	Outpatient	340	0
			Scatter RN Hours	0	0	0
			Offsite Visits	0	0	0

RESEARCH BIONUTRITION	N	MULTICENTER STUDY	N
INFORMATICS CORE	Y	CLINICAL TRIAL	N
BIostatistician	N	CORE LAB	N
ANCILLARIES ONLY	N		

INVESTIGATOR	DEPARTMENT	NON-HOST INSTITUTION: STATE, COUNTRY
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FISHER, JEFFREY D PHD	PSYCHOLOGY	UCONN - STORRS, CT USA
DIECKHAUS, KEVIN MD	Medicine/Infectious Diseases	

SUBPROJECT DESCRIPTION:

Antiretroviral therapy (ART) has enormous promise for reducing Human Immunodeficiency Virus (HIV)-related morbidity and mortality, but ART regimens are often complex, prone to side effects, and expensive, and ART adherence is often extremely poor. The individual and public health consequences of suboptimal ART adherence are significant and include treatment failure, viral load increase, immune compromise, development of multidrug resistant (MDR) HIV, and potential transmission of drug resistant HIV to uninfected others. Although the consequences of suboptimal ART adherence are well-recognized, ART adherence promotion efforts in clinical settings are typically intermittent and ad hoc. When adherence promotion interventions are systematically implemented in clinical care settings, they almost always involve exceedingly time-, cost-, and labor-intensive one-on-one counseling procedures that cannot be widely deployed to assist substantial numbers of HIV+ patients to adhere to ART over time. Moreover, to date, relatively few theory-ART adherence promotion interventions have been conducted, rigorously evaluated, and found to be effective in increasing ART adherence. The present research employs a well-validated conceptualization of health behavior change, the Information-Motivation-Behavioral Skills (IMB) model (J. Fisher & Fisher, 1992, 2000, 2002; W. Fisher & Fisher, 1993, 1999; W. Fisher et al., in press), as a basis for the design and implementation of a cost-, time- and labor-efficient, completely individualized and engaging, computer-assisted ART adherence promotion intervention. The intervention we propose will be employed on an ongoing basis in the context of routine clinical care, to teach adherence enhancement strategies to HIV+ patients about to begin ART, and to increase adherence and maintenance of adherence among HIV+ patients currently on ART.

The proposed research has four specific aims:

1. We will conduct elicitation research with HIV+ patients in clinical care and with HIV care clinicians, to explore the dynamics of ART nonadherence in the HIV+ clinical population, and to identify the optimal structure and content of a theory-based, computer-assisted ART adherence intervention linked to clinical care visits. Elicitation research findings will be systematically integrated to guide the development of the intervention and to increase its ecological validity by adapting it to the dynamics of ART nonadherence among clinic patients, and to the realities of real-life clinical settings.
2. Based on elicitation research findings, guided by the IMB model, and employing motivational interviewing (MI) techniques as an intervention delivery system, we will design, pilot test, refine, and fully implement a theory-based, computer-assisted ART adherence intervention that is linked to naturally occurring HIV clinical care.
3. We will conduct rigorous intervention outcome research comparing the effects of the ART adherence intervention with an appropriate standard-of-care control group with respect to multiple measures of adherence collected over 18 months. Rates of adherence, estimated by three types of indicators (self-reports of adherence to medication, pharmacy refill records, and viral load assessments) will be collected over an 18 month period and will serve as the major outcomes of interest. We hypothesize that participants in the intervention condition will demonstrate better adherence, as defined by greater gains in absolute values of the adherence indicators noted above and by a larger proportion of participants who experience success in achieving and sustaining clinically optimal levels of adherence (e.g., $\geq 95\%$), compared to those in the control condition. Additionally, we predict that

individuals who use the intervention; training arm component before beginning ART will demonstrate better initial degrees of adherence, compared to controls. Finally, we predict that changes in adherence as a result of the intervention will be mediated by intervention effects on ART adherence information, motivation, and behavioral skills.

4. We will use the standard-of-care control group from the intervention outcome research as a no-cost cohort for a longitudinal natural history study of ART adherence in HIV+ patients. We will test putative proximal determinants of adherence to therapy, including levels of adherence-related information, motivation, and behavioral skills. We will also test the influence on adherence of subjective and objective health status, substance use, depressed mental health functioning, changing ART regimens, development of new drugs, and other historical events that may occur over the course of the study. We hypothesize that ART adherence will be predicted longitudinally by ART adherence related information, motivation, and behavioral skills. We also hypothesize that longitudinal trends in adherence will be influenced by factors such as substance use, mental health functioning, and historical events.

SUBPROJECT PROGRESS:

1. A total of 138 participants were recruited for the LifeWindows Study at the University of Connecticut Health Center. Seventy-three participants are in the control condition and 65 are in the intervention condition. Of the 138 participants at UCHC, 54 are men and 84 are women; 101 are Non-Hispanic and 37 are Hispanic; and with respect to race, 55 participants at UCHC are White, 40 are Black/African American, six are of more than one race, and one is American Indian/Alaska Native. The race of 36 participants at UCHC is unknown or was not reported. Finally, of the 138 enrolled participants at UCHC, seven were screened out because they did not meet our requirements, and five participants have dropped out of our study. Across all clinic sites, a total of 676 participants have been recruited (263 women, 408 men, 5 transgender). Of these participants, 64 have been screened out because they did not meet study requirements, and 20 have dropped out of the study. Most of these participants are Non-Hispanic (Non-Hispanic=493; Hispanic=188; Unknown=5), and with respect to race, 289 participants are Black/African American, 204 are White, 51 are of more than one race, and eight are American Indian/Alaska Native. The race of one participant is listed as other," and the race of 123 participants is unknown or was not reported. Please note that our study is closed to recruitment.

2. N/A - Recruitment for the project has finished.

3. There have been no unexpected safety concerns.

4. A significant amount of data has been collected with respect to HIV+ participants' usage of the LifeWindows ART adherence-promotion software program. Details pertaining to LifeWindows usage based on our current baseline data set are as follows: Time Spent Using the LifeWindows Software Program - The main components of the software (a guided survey assessment + intervention for treatment arm and guided survey only for control arm) took 29 minutes (treatment) and 24 minutes (control) at baseline and 29 minutes (treatment) and 16 minutes (treatment), respectively, at follow-up. Adherence Rates at Baseline - In LifeWindows, participants are asked about their adherence to their HIV medications over the last three days and over the last 3-4 weeks. At baseline, 25% of participants reported <95% adherence over the last three days, 26% reported missing at least one dose in the last three days, and 54% reported less than 100% adherence on a global 3-4 week measure of adherence.

Information-Motivation-Behavioral Skills (IMB) Barriers to Adherence - LifeWindows assesses each participant's information, motivation, and behavioral skills (IMB) barriers to adherence during each session. At baseline, the five most frequently reported IMB barriers to adherence and the percentage of HIV+ participants reporting each barrier are as follows: - It upsets me that the HIV meds I have been prescribed can cause side effects. (72%) - I am worried that other people might realize that I am HIV+ if they see me taking my HIV meds. (63%) - It frustrates me to think that I will have to take these HIV meds every day for the rest of my life. (58%) - I understand how each of my HIV meds works in my body to fight HIV. (58%) - I know what the possible side effects of each of my HIV meds are. (58%) Note that the mean number of IMB barriers reported differed between HIV+ participants who missed a dose (15 barriers) and HIV+ participants who had not missed a dose of their HIV medications (12 barriers). IMB Based Adherence Support Strategies After reporting their IMB barriers to adherence, treatment arm participants go on through the LifeWindows program to review a set of adherence support strategies tailored to their specific IMB barriers, and select one that would help the most with adherence. The top four adherence-promotion strategies are as follows: - Learn more about how your HIV medications work in your body. (offered in 55% of sessions, selected in 26%) - Learn about the side effects of your HIV medications and ways to deal with them. (offered in 87% of sessions, selected in 16%) - Learn how skipping you HIV medications from time to time can keep them from working for you and hurt your health. (offered in 53% of sessions, selected in 16%) - Learn how taking your HIV medications as prescribed can help you to live longer. (offered in 11% of sessions, selected in 16%) Intervention Selection and Activities - Based on the adherence support strategy that treatment arm participants select, participants are given a tailored list of adherence-promotion activities/interventions. Twenty targeted activities/interventions are available in LifeWindows. The five most frequently chosen activities at baseline, the percentage of baseline treatment-arm sessions in which these activities were chosen, and brief descriptions of these activities are as follows: Doc Talk (16%) - Offered to those with information, motivation, or behavioral skills deficits, this video-based, interview-style activity allows patients to ask HIV doctors about a broad range of HIV-related issues, including HIV treatment, side effects, and resistance. Journey through the Bloodstream (13%) - Offered to those with deficits in information about HIV medications, this animated documentary style movie explains T-Cells, CD-4 count, HIV, viral load, resistance, types of HIV medications, and how HIV medications fight HIV in the body. Positive Voices (12%) - Offered to those with information, motivation,

or behavioral skills deficits, this video-based activity covers a broad range of topics through unscripted interviews with HIV+ individuals. A variety of strategies for overcoming barriers to adherence are discussed. My Meds (9%) - Offered to those with informational deficits and those who might benefit from increased skills in managing side-effects. This activity provides comprehensive information regarding one's specific HIV medications; side effects, drug interactions, and dietary restrictions for each medication. Celebrate Success (9%) - Offered to those with perfect adherence, this activity promotes maintenance of perfect adherence by focusing on the importance of recognizing and rewarding this accomplishment. This activity also covers issues germane to relapse prevention. Goal Setting - After completing an activity, an adherence-related, activity-specific goal is selected by the user, and he or she is asked to try to accomplish this goal before the next LifeWindows session. On follow-up sessions, 31% of treatment arm participants reported partially accomplishing their goal, while 61% reported accomplishing it completely. Interim Conclusions - The LifeWindows software program is being used as intended, with full treatment sessions averaging about 30 minutes. We are continuing to collect data through our LifeWindows software program, and thus far, these data suggest that not only do patients taking HIV medications demonstrate a wide variety of barriers to adherence, but these patients also differ in their preferences with respect to the types of activities/interventions they are choosing to help with their adherence-related needs. Recognizing the diversity in HIV+ individuals' adherence-related needs and using a choice-driven ideographic intervention approach may prove to be a key step toward improving and maintaining optimal ART adherence.

5. While the protocol has not changed over the last year, we are in the process of creating an addendum to the informed consent forms and adding an 'exit survey' to the currently approved set of research measures. The addendum to the informed consent specifically clarifies the data-collection end date of the project, so that enrolled participants are fully aware of the maximum amount of time they will be able to participate in the project. On the original consent forms participants were advised that project participation would be for 18 months. The addendum to the consent forms clearly specifies start and end dates for participation in the LifeWindows project. Clarification of 'start date' is important for participants who (1) were consented or enrolled in the project several months prior to their first use of the LifeWindows software and/or (2) were temporarily discontinued from antiretroviral therapy (ART) when they began using LifeWindows. Start-date is considered the date of the first full LifeWindows session, and not consent or enrollment date or date for initial sessions where the participant was not actively prescribed antiretroviral therapy (ART). For participants who began using LifeWindows while on a prescribed interruption of ART, their first full LifeWindows session would not be until they were back on ART. Clarification of 'end date' is also important for those participants whose 18-months of participation will exceed the project end-date. The project end-date is March 2008. After March 2008, no further LifeWindows sessions will be offered at the clinics. In cases where the participant's 'start date' is after October 2006, they will not have the opportunity to participate in the project for a full 18 months because of the project end-date and their total length of active participation in the project will be truncated. The addendums to the treatment and control arm informed consents clearly specify the start and end date requirements of participation. Additionally, we anticipate submitting an addendum to the informed consent for acquiring pharmacy refill data: specifically, we request that participants consent to retrieving such data relative to the start and end dates of the formal research project, instead of relative to their specific enrollment and end dates. In practice, we have determined that retrieval of pharmacy refill information is greatly facilitated by the use of a single start date for the entire sample. Because rates of adherence from pharmacy refill records require approximately 3 months of activity, we are requesting that participants consent to records reviews that begin in December 2004 (3 months prior to the formal project's start date) to June 2008 (3 months post the formal project's end date). In addition to the informed consent addendums, we plan to add a brief paper and pencil measure to the set of approved research instruments. This measure is designed as an 'exit survey' and asks participants who are preparing to complete their participation in the LifeWindows project important questions about their overall experiences with the software and in the overall project. These quality-assurance items are marked only by the participant's random identification number, completed in clinic, and sealed for privacy. Once approved by appropriate review boards, this measure will be given to participants who have 3 months of project participation remaining.

6. We are at the end of our baseline data collection period and we will very soon be in a position to develop and submit manuscripts based on these data.

SPID: 0582	PROTOCOL: 582	TYPE: RESEARCH
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SHORT TITLE: Brain Changes and Risk Factors

LONG TITLE: Brain Changes and Risk Factors

AIDS:	N	TOTALS	A	B	D
		Inpatient	0	0	0
START DATE:	4/28/2005	Scatter Bed	0	0	0
Total # pts expected for entire study:	99	Outpatient	21	0	0
		Scatter RN Hours	0	0	0
		Offsite Visits	0	0	0

RESEARCH BIONUTRITION	N	MULTICENTER STUDY	N
INFORMATICS CORE	N	CLINICAL TRIAL	N
BIostatistician	N	CORE LAB	Y
ANCILLARIES ONLY	N		

INVESTIGATOR	DEPARTMENT	NON-HOST INSTITUTION: STATE, COUNTRY
WOLFSON, LESLIE MD	Medicine/Neurology	
CALHOUN, VINCE D MD	PSYCHIATRY	YALE UNIVERSITY, CT USA
GUTMAN, CHARLES MD	CNTR FOR NEUROLOGICAL IMG	BRIGHAM & WOMENS HOSPITAL, MA USA
KAPLAN, RICHARD PHD	Psychiatry	
PANZER, VICTORIA MD	Neurology	
PEARLSON, GODFREY D MD	PSYCHIATRY	INSTITUTE OF LIVING, CT USA
WAGNER, JULIE PHD	Behavioral Sci & Comm Hlth	
WARFIELD, SIMON K PHD	RADIOLOGY	BRIGHAM & WOMEN'S HOSPITAL, MA USA
WHITE, WILLIAM MD	Medicine/Hypertension	

SUBPROJECT DESCRIPTION:

Mobility is a critical component of independence and the quality of life of older persons. A significant number of older persons with mobility impairment demonstrate ischemic lesions in brain white matter (WM).

We hypothesize that: Students with a high level of vascular disease risk factors, will have a larger initial volume and higher accrual rate of white matter signal abnormality (WMSA); impaired mobility is caused by site-specific WMSA damaging fronto-parietal periventricular WM and WMSA accrual rate is stable allowing predication of Ss at risk" for large WMSA increases. The link between ischemic WM lesions, which appear on MRI as WM signal abnormality (WMSA), and vascular disease risk factors (VDRF), as a cause, requires better definition. We propose to link VDRF to mobility impairment associated with WMSA and then determine if the risk factors predict incident cases. This will allow us to assess the magnitude of the VDRF as a cause of mobility impairment in order to plan new treatment strategies.

We will use quantitative Magnetic Resonance Imaging (MRI) and quantitative measures of mobility to link WMSA to mobility disorders. In preliminary studies, we separated older persons into groups with normal and impaired mobility. Automated quantitative segmentation of the MR images showed an accrual of WMSA is related to a disease process. Site-specific periventricular WMSA involving frontal and parieto-occipital regions were present in Students with impaired mobility. Follow-up MRIs on 14 Students, 20 months after the initial scan, showed WMSA accrual was related to WMSA volume at baseline suggesting a continuous process and that the volume of WMSA increased at a five-fold greater rate in mobility impaired compared to normal Students. We have recently determined that the quantitative measures of mobility are reliable. To move beyond correlation, we are proposing a 5-year project with 2 components: a cross-sectional analysis of 99 Students 70 years and older stratified by mobility, followed by a 4 year longitudinal follow-up.

The cross-sectional component will determine the relationship of VDRF, WMSA volume, WMSA location, use diffusion tensor imaging to identify/quantify damage to WM pathways and quantitative measures of mobility. Using the same measures, the longitudinal component will: 1) establish the link between VDRF and mobility impairment; 2) establish clinical predictive value of imaging; 3) evaluate the causal relationship of WMSA to mobility; 4) refine our understanding of the anatomic substrate of mobility

impairment; and 5) define the progression of this disorder.

SUBPROJECT PROGRESS:

Our study closed recruitment at 99 subjects, following the enrollment of the last 19 subjects in the reporting period. We have had 6 subjects terminate participation: 3 have had pacemakers installed and can no longer have an MRI, 2 have died (of natural causes) and 1 is not interested in participating. We are looking to modify our protocol and re-open enrollment to counter attrition effects. While we have a conservative rate of attrition built into the study, we are concerned that the rate may be more significant. The recruitment of additional subjects will not exceed the originally proposed goal of 105 subjects, and therefore will not affect the budgeted costs for the study. Our 2-year assessments are scheduled to begin on June 1. We will also be modifying our proposal to add the collection of amyloid beta and creatinine. We have not encountered any unexpected safety concerns, and baseline data is still in the process of being analyzed. There have not been any papers accepted for publication although Dr. Moscufo and Dr. Panzer have papers in the submission process. Dr. White wrote an editorial on the relationship of nocturnal blood pressure and white matter lesions (Hypertension. 2007;49:1-2). The GCRC was not cited on this editorial as it did not reference study results.

SPID: 0583 **PROTOCOL:** 583 **TYPE:** RESEARCH

SHORT TITLE: NSABP B-37

LONG TITLE: NSABP B 37: A Randomized Clinical Trial of Adjuvant Chemotherapy for Radically Resected Loco-Regional Relapse of Breast Cancer

AIDS:	N	TOTALS	A	B	D
			Inpatient	0	0
START DATE:	4/28/2005	Scatter Bed	0	0	0
Total # pts expected for entire study:	10	Outpatient	0	0	0
		Scatter RN Hours	0	0	0
		Offsite Visits	0	0	0

RESEARCH BIONUTRITION	N	MULTICENTER STUDY	Y
INFORMATICS CORE	Y	CLINICAL TRIAL	N
BIostatistician	N	CORE LAB	N
ANCILLARIES ONLY	N		

INVESTIGATOR	DEPARTMENT	NON-HOST INSTITUTION: STATE, COUNTRY
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KURTZMAN, SCOTT MD	Surgery	
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SUBPROJECT DESCRIPTION:

Local and regional recurrences of invasive breast cancer occur in 10-30% of patients after adequate radical local treatment. Adjuvant radiation therapy diminishes the risk of local recurrence substantially as does adjuvant systemic therapy. The annual risk of developing a local recurrence is 2% after breast conserving surgery with adjuvant radiation therapy and 0.5-1% after mastectomy. Overall, about 50% of patients develop recurrent disease (local or systemic), and 30-40% of patients die from metastatic disease breast cancer within 5 years after recurrence. Adjuvant chemotherapy reduces the risk of recurrence after primary breast cancer. It would seem obvious to postulate reasonable to expect that secondary adjuvant chemotherapy (after a recurrence) would also diminish the risk of recurrence after radical treatment of isolated local and regional recurrences of breast cancer. There have been only a few randomized trials of adjuvant systemic therapy for local and regional recurrent breast cancer, but they have not really defined the role of chemotherapy in the isolated loco-regional recurrent setting. Chemotherapy is, however, a promising treatment option for such patients, and an increasing number of drugs have become available that could be investigated. The randomization process will simply allocate the patients to chemotherapy or follow-up without chemotherapy after adequate local treatment of the recurrence. To ensure adequate participation in the trial the choices of surgical procedure, radiation therapy techniques and the drugs used for the chemotherapy are at the discretion of the treating clinician; the randomization process will simply allocate the patients to chemotherapy or follow-up without chemotherapy. The trial objectives are to evaluate the efficacy of adjuvant chemotherapy after radical local treatment of a first loco-regional recurrence of breast cancer. Treatment comparisons will be based upon the following endpoints: 1) disease free survival (primary endpoint); 2) overall survival and systemic disease free survival; and 3) quality of life.

SUBPROJECT PROGRESS:

This study has been terminated. We never enrolled subjects on this trial.

SPID: 0585	PROTOCOL: 585	TYPE: RESEARCH
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SHORT TITLE: PACTG P1059

LONG TITLE: Pediatric Aids Clinical Trials Group (PACTG) P1059: A Phase I, Open-Label Study to Evaluate the Safety and Tolerability of Recombinant HIV-1 Vaccines in HIV-1 Infected Young Adults

AIDS:	Y	TOTALS	A	B	D
			Inpatient	0	0
START DATE:	6/16/2005	Scatter Bed	0	0	0
Total # pts expected for entire study:	2	Outpatient	0	0	0
		Scatter RN Hours	0	0	0
		Offsite Visits	0	0	0

RESEARCH BIONUTRITION	N	MULTICENTER STUDY	Y	
INFORMATICS CORE	Y	CLINICAL TRIAL	Y	Phase I
BIostatistician	N	CORE LAB	N	
ANCILLARIES ONLY	N			

INVESTIGATOR	DEPARTMENT	NON-HOST INSTITUTION: STATE, COUNTRY
SALAZAR, JUAN C MD	PEDIATRICS	
FEDER, HENRY MD	Medicine/Family Medicine	
KRAUSE, PETER MD	Pediatrics	

SUBPROJECT DESCRIPTION:

PACTG 1059 is a phase I study which will evaluate the safety and tolerance of Human Immunodeficiency Virus (HIV)-1 recombinant vaccines in young adults. Children and young adults with HIV-infection have been shown to have relative preservation of thymic function with improved ability to respond to new antigens as compared to older adults. Therefore, the age group of 18-24 years is a reasonable population to evaluate safety and to inform future studies for HIV infected children, adolescents and adults. Once safety is established in this group, further studies will be considered to assess safety in other patient populations and immunogenicity can be further evaluated. Ultimately, these candidate vaccines have potential to be useful as prophylactic and therapeutic vaccines. If the results of the present studies support safety of these products in this patient population, further studies to evaluate potential as therapeutic vaccines will be planned in children, adolescents and young adults.

Subjects will receive two pairs of matching recombinant HIV-1 vaccines that utilize a modified vaccinia Ankara (MVA) vector and a fowlpox vector (FPV) (Therion Biologics Corp.). Each vector pair contains identical HIV-1 inserts, one consisting of env/gag and the other of modified tat/rev/nef-RT, derived from a vertically transmitted pediatric primary isolate (C58A1, clade B).

The HIV-1 sequences utilized by Therion were isolated at the University of Massachusetts Medical Center from a vertically HIV-1-infected infant by polymerase chain reaction (PCR) amplification of proviral Deoxyribonucleic acid (DNA) derived from peripheral blood mononuclear cells, and were designated as HIV-1 strain C58A1 (subtype B, primary isolate). The env gene expressed by the vaccines contains the immunodominant portion of gp41. The tat, rev, nef and reverse transcriptase (RT) genes were modified in order to render the proteins non-functional. The mutated tat protein was tested in a transactivation system and was unable to activate the transcription of HIV-1- long terminal repeat (LTR). The nef-RT fusion gene was tested in a colorimetric immunoassay for retroviral RT activity; no enzymatic activity was detected. These genes were inserted into two MVA and two FPV vectors, one of each pair containing env and gag, and the other containing tat, rev, and a nef-RT fusion gene.

SUBPROJECT PROGRESS:

ACTG 1059 (Version 1.0) has had no enrollments in the report period, and no enrollments since the initiation of the study.

Due to funding changes throughout the PACTG/IMPAACT Network, we will no longer be able to offer this protocol.

SPID: 0586 **PROTOCOL:** 586 **TYPE:** RESEARCH

SHORT TITLE: Transposon-Based Functional Analysis
LONG TITLE: Transposon-Based Functional Analysis of Malaria Genome

AIDS:	N	TOTALS	A	B	D
		Inpatient	0	0	0
START DATE:	6/16/2005	Scatter Bed	0	0	0
Total # pts expected for entire study:	120	Outpatient	13	0	0
		Scatter RN Hours	0	0	0
		Offsite Visits	0	0	0

RESEARCH BIONUTRITION	N	MULTICENTER STUDY	N
INFORMATICS CORE	N	CLINICAL TRIAL	N
BIostatistician	N	CORE LAB	N
ANCILLARIES ONLY	N		

INVESTIGATOR	DEPARTMENT	NON-HOST INSTITUTION: STATE, COUNTRY
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BENMAMOUN, CHOUKRI MD Microbial Pathology

SUBPROJECT DESCRIPTION:

Malaria, a disease caused by protozoan parasites of the genus Plasmodium, is one of the most dangerous infectious disease affecting human populations. The purpose of this research is to determine the conditions that help the multiplication of the parasite in human red blood cells. The scientific information received from this study may help understand the disease and identify new drugs or a vaccine against malaria.

Research in the Lab will focus on how the Human Malaria Parasite develops within human red blood cells. Our goal is to characterize, at the molecular level, the pathways essential for the parasites survival with an eye toward future drug development.

SUBPROJECT PROGRESS:

Number of subjects enrolling during the report period: 11 subjects (13 blood draws) - Number of subjects enrolling since initiation of the study: 18 subjects (26 blood draws) - Any changes in recruitment plans that might be needed: NO - Unexpected safety concerns and their resolution: NO - Interim data and outcomes if appropriate: N/A - Any proposed changes made or anticipated in the protocol: NO - Publications, indicating whether the GCRC was cited:

SPID: 0587 **PROTOCOL:** 587 **TYPE:** RESEARCH

SHORT TITLE: Nucleoside Transporters
LONG TITLE: Nucleoside Transporters of Plasmodium Falciparum

AIDS:	N	TOTALS	A	B	D
		Inpatient	0	0	0
START DATE:	6/16/2005	Scatter Bed	0	0	0
Total # pts expected for entire study:	25	Outpatient	26	0	0
		Scatter RN Hours	0	0	0
		Offsite Visits	0	0	0

RESEARCH BIONUTRITION	N	MULTICENTER STUDY	N
INFORMATICS CORE	N	CLINICAL TRIAL	N
BIostatistician	N	CORE LAB	N
ANCILLARIES ONLY	N		

INVESTIGATOR	DEPARTMENT	NON-HOST INSTITUTION: STATE, COUNTRY
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BENMAMOUN, CHOUKRI MD	Microbial Pathology	
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SUBPROJECT DESCRIPTION:

Malaria, a disease caused by protozoan parasites of the genus Plasmodium, is one of the most dangerous infectious disease affecting human populations. The purpose of this research is to determine the conditions that help the multiplication of the parasite in human red blood cells. The scientific information received from this study may help understand the disease and identify new drugs or a vaccine against malaria. Research in the Lab will focus on how the Human Malaria Parasite develops within human red blood cells. Our goal is to characterize, at the molecular level, the pathways essential for the parasite survival with an eye toward future drug development.

SUBPROJECT PROGRESS:

Number of subjects enrolling during the report period: 7 subjects (23 blood draws) - Number of subjects enrolling since initiation of the study: 19 subjects (33 blood draws) - Any changes in recruitment plans that might be needed: increase enrollement to 35 subjects - Unexpected safety concerns and their resolution: NO - Interim data and outcomes if appropriate: N/A - Any proposed changes made or anticipated in the protocol: NO - Publications, indicating whether the GCRC was cited: Kamal ELBISSATI, Rachel ZUFFEREY, William H. WITOLA, Nicola S. CARTER, Buddy ULLMAN, and Choukri BEN MAMOUN. The Plasma Membrane Permease PfNT1 is Essential for Purine Salvage in the Human Malaria Parasite Plasmodium falciparum. (2006) PNAS, 103: 9286-9291.

SPID: 0588 **PROTOCOL:** 588 **TYPE:** RESEARCH

SHORT TITLE: Assessing Osteoporosis Risk
LONG TITLE: Assessing Osteoporosis Risk in Frail Older Adults

AIDS:	N	TOTALS	A	B	D
			Inpatient	0	0
START DATE:	6/16/2005	Scatter Bed	0	0	0
Total # pts expected for entire study:	158	Outpatient	0	0	0
		Scatter RN Hours	0	0	0
		Offsite Visits	1	0	0

RESEARCH BIONUTRITION	N	MULTICENTER STUDY	N
INFORMATICS CORE	N	CLINICAL TRIAL	N
BIostatistician	Y	CORE LAB	Y
ANCILLARIES ONLY	N		

INVESTIGATOR	DEPARTMENT	NON-HOST INSTITUTION: STATE, COUNTRY
KENNY, ANNE M MD	CENTER ON AGING	
CABRAL, CYNTHIA BS	Dental-Students	
SMITH, JOANNE MD	Medicine	
WAYNIK, ILANA MD	Pediatrics	

SUBPROJECT DESCRIPTION:

Little research has been done to assess the level of osteoporosis evaluation or diagnosis, bone mass measurement or contributors to bone loss and fall risk in residents of assisted living communities. Hypotheses and Specific Aims 1) Individuals residing in assisted living will have a low rate of osteoporosis evaluation or diagnosis relative to community dwelling elders. We will survey individual for history and evaluation of osteoporosis in assisted living and compare to a group of age and gender matched community dwelling adults 2) Individuals residing in assisted living will have low bone mass, measured by heel ultrasound, compared to community dwelling elders. Quantitative ultrasound will be used to assess bone mass. 3) The stiffness index T score will correlate with calcitropic hormones (directly with 25OHD and inversely with PTH) and directly to physical performance measures (hand grip, walking speed and physical activity). Study Design: Cross-sectional analysis of 79 residents of assisted living with a comparison to 79 age and gender-matched community dwelling adults. Research volunteers will undergo bone assessment using heel ultrasound, questionnaires to assess fracture history and previous osteoporosis evaluation, falls in previous 6 months, dietary intake of calcium, vitamin D and protein, and will have physical performance measures including hand grip strength and walking speed. In a previous study of 55 community dwelling older men (mean age 73 + 8 y), correlations were found between stiffness index T score and physical activity score ($r=.30, p=.043$), walking speed ($r=-.37, p=.006$) and a trend with handgrip ($r=.24, p=.07$). Based on this previous work, we calculate that we will need to assess 158 subjects. The proportion of underserved individuals in the assisted-living, elderly population will be contrasted with that in the healthy, non-assisted-living, older population using contingency table methods. The frequency of osteoporosis detected by heel ultrasound will be calculated and compared to established, national, age-adjusted, prevalence estimates. Correlation analysis will be used to evaluate associations between heel ultrasound, bone mineral density, vitamin-D levels, parathyroid hormone levels, and frailty measures. For the contrast of proportions, samples of 79 assisted-living subjects and 79 non-assisted-living subjects will provide 80% power to detect odds ratios of 3.0 or more when testing at the 5% level of significance. When combined, those samples will also provide 80% power to detect correlation coefficients greater than +0.22 or smaller than -0.22. pard

SUBPROJECT PROGRESS:

We completed enrollment for the study -- we recruited a total of 114 individuals (4 more since last update). There were no safety concerns. The data is currently being analyzed for publication. We will continue to need statistical support.

SPID: 0589 **PROTOCOL:** 589 **TYPE:** RESEARCH

SHORT TITLE: Individualized Assessment and Treatment for Alcohol

LONG TITLE: Individualized Assessment and Treatment for Alcohol (IATP)

AIDS:	N	TOTALS	A	B	D
		Inpatient	0	0	0
START DATE:	7/20/2005	Scatter Bed	0	0	0
Total # pts expected for entire study:	120	Outpatient	63	0	0
		Scatter RN Hours	0	0	0
		Offsite Visits	0	0	0

RESEARCH BIONUTRITION	N	MULTICENTER STUDY	N
INFORMATICS CORE	Y	CLINICAL TRIAL	N
BIostatistician	N	CORE LAB	N
ANCILLARIES ONLY	N		

INVESTIGATOR	DEPARTMENT	NON-HOST INSTITUTION: STATE, COUNTRY
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LITT, MARK D PHD	BEHAVIORAL SCI & COMM HLTH	
COONEY, NED L PHD	PSYCHIATRY	YALE UNIVERSITY, CT USA
KADDEN, RONALD M PHD	Psychiatry	

SUBPROJECT DESCRIPTION:

Despite the popularity of Cognitive-Behavioral Treatment (CBT) in substance use disorders, recent findings have indicated that CBT may be no more effective than other, less theoretically driven, treatments, and that CBT treatments often fail to result in coping skills acquisition. In order to explore the possibility that current manual-driven modes of CBT delivery may not be adequate to successfully teach coping skills, we are proposing a pilot project for the development of an individualized assessment and cognitive-behavioral treatment program (IATP) for alcohol-dependent persons, in which experience sampling conducted via random calls to cell-phones is used to provide data to create individualized treatment plans. Data collected during experience sampling will include momentary assessments of patients cognitions, affects, and coping behaviors with respect to drinking.

Participants will be 112 men and women meeting criteria for alcohol dependence or alcohol abuse, who will be randomly assigned to either a standard packaged manual-driven cognitive-behavioral treatment program (PCBT) like that used in Project MATCH, or to IATP. Patients in both treatments will be asked to engage in experience sampling for two weeks prior to treatment, and for another two weeks after treatment has ended, in order to compare in-vivo measures of coping skills utilization, pre- and post-treatment, between the two groups. Therapy will be conducted over 12 sessions in both treatments.

In IATP, the information gathered from experience sampling will form the basis of a functional analysis of patients' drinking and drinking urges during the monitoring period. Cognitive appraisals, moods and coping responses will be evaluated as antecedents and consequences of drinking behavior. Therapists will use the information to address specific cognitions, affects, and behaviors that are adaptive and maladaptive, and will work with the patient to substitute adaptive coping tactics instead.

In PCBT the experience sampling data will not be specifically used in therapy, but will still provide in-vivo measures of drinking and coping skills. It is hypothesized that IATP will yield significantly better coping skills acquisition than will PCBT, and that change in coping skills will predict better post treatment outcomes for IATP. These results would have implications for our delivery of treatment, and for the validity of coping skills training for alcohol addiction.

Specific Aims are as follows:

1. To determine whether an Individualized Assessment and Treatment Program (IATP) results in greater acquisition of coping skills than does a standard Packaged Cognitive-Behavioral Treatment (PCBT).

H1: It is hypothesized that IATP will result in significantly greater increases in reported use of coping skills from pre- to post-treatment relative to PCBT.

2. To determine if coping skills acquisition in IATP accounts for treatment outcome over and above the contribution made by pretreatment individual differences (i.e., motivation and self-efficacy).

H2: It is hypothesized that pre- to post-treatment increases in coping skills in the IATP condition will account for more variance in

drinking outcomes at post-treatment than will pretreatment individual difference variables.

3. To determine whether IATP, based on functional analysis of in-vivo patient monitoring, will yield better outcomes at post-treatment than will PCBT

H3: It is hypothesized that IATP will yield better drinking outcomes at post-treatment than will the standard packaged CB approach. Drinking outcomes will include proportion days abstinent, and proportion heavy drinking days during the treatment period.

SUBPROJECT PROGRESS:

94 patients enrolled in the study thus far, 78 enrolled in this study period. No changes in recruitment plans needed. No safety concerns. No interim data available as yet. No changes in protocol made or anticipated. No publications available.

SPID:	0590	PROTOCOL:	590	TYPE:	RESEARCH	
SHORT TITLE:	Pregnancy Stress					
LONG TITLE:	Longitudinal Measurement of Work Stressors in Pregnancy					
AIDS:	N	TOTALS		A	B	D
		Inpatient		0	0	0
START DATE:	7/21/2005	Scatter Bed		0	0	0
Total # pts expected for entire study:	200	Outpatient		0	0	0
		Scatter RN Hours		0	0	0
		Offsite Visits		56	0	0
RESEARCH BIONUTRITION	N	MULTICENTER STUDY		N		
INFORMATICS CORE	Y	CLINICAL TRIAL		N		
BIostatistician	N	CORE LAB		Y		
ANCILLARIES ONLY	N					

INVESTIGATOR	DEPARTMENT	NON-HOST INSTITUTION: STATE, COUNTRY
MEYER, JOHN D MD, PHD	OCCUPATIONAL MEDICINE	
NICHOLS, GINGER MS	Human Genetics	
O'CAMPO, PATRICIA PHD	MATERNAL/CHILD HEALTH	U OF TORONTO, CANADA
WARREN, NICHOLAS PHD	Occupational Medicine	

SUBPROJECT DESCRIPTION:

Evidence suggests that some groups of pregnant workers may be at risk for premature delivery or small-for-gestational-age (SGA) births as a consequence of workplace psychosocial stressors. Clear associations between occupational stressors and adverse pregnancy outcomes have been difficult to draw. Factors including study design, retrospective assessment of exposure, and choice of exposure measurement may be partially obscuring any association between work-related stress and pregnancy outcomes.

The overall goals of this proposed developmental and planning grant are to obtain preliminary data assessing two models of occupational stress during pregnancy, in particular measuring repeatedly and longitudinally across the course of pregnancy to evaluate the possibility that these may change across pregnancy. This proposal aims also to evaluate the use of the effort-reward imbalance (ERI) model, which has not been tested in pregnant workers or used in studies of pregnancy outcomes.

Using a sample of 200 pregnant working women, this study proposes repeated, longitudinal measures of occupational stress at four different times across the course of pregnancy.

Principal aims of the study are:

- 1) To explore the use of newer instruments measuring occupational psychosocial stressors in pregnant women; specifically using the Effort-Reward Imbalance (ERI) model, with comparison to, and possible combination of features with, the Demand-Control (DC) model.
- 2) To evaluate the psychometric properties of the ERI in pregnancy, including reliability, and content validity.
- 3) To evaluate the construct validity of the stress scales, to enable their use in measuring occupational psychosocial strain in pregnancy.
- 4) To evaluate the possibility that occupational psychosocial stressor levels in working women change across the unique time period represented by pregnancy, assessing the direction and magnitude of this change. Statistical methods for repeated-measures and hierarchical data will be used to examine trajectories of occupational stressors as well as their possible modification by other individual-level factors. Outcomes will be measured by subjects' measures of their stress, health, and fatigue, as well as blood pressure measurements and salivary cortisol levels. The work proposed here represents a necessary first step in the ability to test these hypothesized effects, and will assist in determining whether newer models of the psychosocial parameters of stress in the workplace might be useful in measuring an association with adverse pregnancy outcomes.

As well, this work will represent an initial assessment of whether changes in measured parameters of stress, or distinct trajectories over time, occur during the course of pregnancy. Once these aims are accomplished, the resultant exposure measurements can be used in ongoing studies to recognize and target particular types of work that may be associated with adverse birth outcomes. The exploratory work proposed here may enhance understanding of special populations at risk from work stressors.

SUBPROJECT PROGRESS:

This study which effectively started in early 2006 began recruiting in the spring of 2006. During the reporting period, approximately 40 subjects have been recruited and completed at least one interview. Data are collected on scannable questionnaire forms; initial data on the first 30 subjects has just been scanned and recieved. Analysis has not yet begun. Cortisol samples have been collected and will be analyzed when an appropriate number have been assembled; likely for uniformity and convenience at the end of the study. As a consequence, preliminary data cannot be shown at this time. Recruitment strategies were expanded in response to an initial low response among potential subjects; these include use of vehicles such as frequent e-mail blasts within the Health Center, postings on the UConn intranet and the General Clinical Research Center site, and endorsement by related organizations such as the UCHC Women's Health centers; this was extended to weekly local newspapers in the Hartford area in the spring of 2006. There have been no unexpected safety concerns or problems during the performance of this study to date. No changes have been made or are anticipated in the protocol. As the study remains in data collection stages, no publications have been completed or are in progress.

SPID: 0591 **PROTOCOL:** 591 **TYPE:** RESEARCH

SHORT TITLE: Women

LONG TITLE: Lifetime History of Major Depressive Disorder and Endothelial Function in Postmenopausal Women

AIDS:	N	TOTALS	A	B	D
		Inpatient	0	0	0
START DATE:	7/25/2005	Scatter Bed	0	0	0
Total # pts expected for entire study:	200	Outpatient	33	0	0
		Scatter RN Hours	0	0	0
		Offsite Visits	0	0	0

RESEARCH BIONUTRITION	N	MULTICENTER STUDY	N
INFORMATICS CORE	Y	CLINICAL TRIAL	N
BIostatistician	N	CORE LAB	Y
ANCILLARIES ONLY	N		

INVESTIGATOR	DEPARTMENT	NON-HOST INSTITUTION: STATE, COUNTRY
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WAGNER, JULIE PHD	Behavioral Sci & Comm Hlth	
MANSOOR, GEORGE MD	Medicine/Hypertension	
TENNEN, HOWARD PHD	Community Medicine	

SUBPROJECT DESCRIPTION:

Major depressive disorder is a well-established risk factor for incident coronary heart disease and women have higher rates of major depressive disorder than their male counterparts. Endothelial functioning is impaired during current depressive episode. However, it is unknown whether this impairment continues once the depressive episode resolves. The overarching question this study asks is whether previous (but specifically not current) major depressive disorder is associated with endothelial dysfunction in post-menopausal women.

This retrospective, controlled study will investigate the relationship between previous major depressive disorder and current coronary heart disease risk in postmenopausal women who are matched for age and Bone Mass Index (BMI). The independent variable is previous major depressive disorder. A reliable, valid, and widely used method for assessing previous behaviors, the timeline follow back method, has been adapted for use with the gold standard diagnostic interview (SCID) to assess previous major depressive disorder. The dependent variable is brachial artery flow mediated dilation. Specific aims are to:

1. Determine whether currently nondepressed women who have experienced previous major depressive disorder have impaired flow mediated dilation relative to their never depressed counterparts. We hypothesize that currently non-depressed women who have experienced previous major depressive disorder will have impaired flow mediated dilation relative to their never depressed counterparts.
2. Determine whether there is a 'dose-response' relationship between number of depressive episodes over the lifespan and flow mediated dilation. We hypothesize that more depressive episodes over the lifespan will be related to decreased flow mediated dilation.
3. Determine whether treatment for depression attenuates any deleterious effects that depression exerts on flow mediated dilation. We hypothesize that previously depressed women whose depression was treated pharmacologically will have less impaired flow mediated dilation than their counterparts whose depression was untreated.

SUBPROJECT PROGRESS:

From 4/1/2006 until 3/31/2007, recruitment began for this study and 20 women enrolled. One woman was excluded from the study after Informed Consent Form (ICF) was obtained and during first visit data collection, for a total of 19 eligible participants during this time period. This was because it was discovered during first visit that they did not meet set criteria to complete the study. Modifications to the project approved by Institutional Review Board (IRB) this year include: 1) A partial waiver of consent solely for the phone screen phase of the study 2) A change in inclusion criteria to expand age of participation from age 80 to age 90. Subjects over age 90 will be excluded from participation 3) A change to protocol shortening amount of time the ultrasound study will take 4) Change in site for ultrasound study from radiology to the General Clinical Research Center (GCRC), to be conducted with study nurse and ultrasound tech from cardiology 5) Addition of 5 standardized self-report assessments to survey packet 6) Approval of a change in staff removing Dr. George Mansoor (who is no longer with University of Connecticut Health Center (UCHC)) from the study team. Drs. William White and Madhavi Mallareddy were added as co-investigators 6) Changes were made to ICF and protocol to reflect the above changes. There are no unexpected safety concerns. There are no publications from this study at this time.

SPID:	0592	PROTOCOL:	592	TYPE:	RESEARCH	
SHORT TITLE:	Canker Sores					
LONG TITLE:	Prevention of Recurrent Aphthous Stomatitis Using Vitamins					
AIDS:	N	TOTALS		A	B	D
		Inpatient		0	0	0
START DATE:	7/28/2005	Scatter Bed		0	0	0
Total # pts expected for entire study:	120	Outpatient		311	0	0
		Scatter RN Hours		0	0	0
		Offsite Visits		0	0	0

RESEARCH BIONUTRITION	N	MULTICENTER STUDY	N
INFORMATICS CORE	N	CLINICAL TRIAL	N
BIostatistician	N	CORE LAB	N
ANCILLARIES ONLY	N		

INVESTIGATOR	DEPARTMENT	NON-HOST INSTITUTION: STATE, COUNTRY
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LALLA, RAJESH V BDS, PHD	ORAL DIAGNOSIS	
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SUBPROJECT DESCRIPTION:

Recurrent aphthous stomatitis (RAS), also known as canker sores, is the most common soft tissue disease of the mouth in humans in all geographic regions, including Connecticut. In a large study of over 10,000 young adults, 38.7% of men and 49.7% of women reported two or more previous occurrences of RAS. These ulcerations are painful and affect the patient's ability to eat and drink.

Further, they may also impact on oral hygiene practices and speech. Thus, RAS has a significant effect on the patient's quality of life. There is currently no known method to prevent RAS. Topical and/or systemic steroids are sometimes used for the treatment of this condition. However, because these drugs have significant side-effects, they are used only for the treatment of the most severe cases. The vast majority of patients with RAS do not have any scientifically validated options for prevention or treatment. Several studies have demonstrated that patients with RAS are more likely to have lower blood levels of vitamins, such as B12 and folic acid, compared to healthy controls. More importantly, multiple studies have demonstrated that specific replacement therapy to correct such deficiencies is effective in inducing improvement or remission of this disease.

A workshop convened by the National Institutes of Health (NIH) recommended complete hematologic screening of all patients with RAS. However, testing for vitamin deficiencies is invasive and expensive. It is not feasible to take blood samples on every patient with RAS and test for such deficiencies. Therefore, this is rarely done in practice and patients continue to suffer from these lesions.

This study proposes an alternative approach: To prevent RAS using a multivitamin supplement that would correct any deficiencies of factors known to commonly contribute to RAS. If successful, this would result in a simple, cost-effective approach to reducing the morbidity of this prevalent disease.

We propose a double-blind, placebo-controlled clinical study in 120 subjects who suffer from RAS. Subjects will be randomly assigned to either a multivitamin supplement or an inactive placebo, in a 1:1 ratio (60 in each group). The study medication will be taken once a day for one year. We will document, in all subjects, the number of RAS episodes in one year and the duration of episodes. These will be compared between the two groups to find out if the multivitamin supplement was effective in reducing the number or duration of RAS episodes. We will also collect data on pain and normalcy of diet during RAS episodes to determine if the multivitamin supplement had any effect on these variables.

To enhance subject compliance and retention, we will use Interactive Voice Response (IVR) technology that uses the telephone to administer survey questions. A blood sample will be collected from all consenting subjects at baseline. This blood sample will be used to measure the baseline levels of vitamins B12 and B9 (folic acid). These are the principal vitamins whose deficiency has been associated with RAS. All subjects will be asked to complete a Diet History Questionnaire at the beginning and at the end of the study. The purpose of this questionnaire is to estimate dietary intake of the vitamins being supplemented, at baseline and over the one-year period of the study.

SUBPROJECT PROGRESS:

Number of subjects enrolling during the report period: 79 and since initiation of the study: 100 - Any changes in recruitment plans that might be needed: Due to the high number of dropouts to date (18), we are in process of requesting IRB permission to increase enrollment to up to 160 subjects, an increase of up to 40 subjects. - Unexpected safety concerns and their resolution: None - Interim data and outcomes if appropriate: None - Any proposed changes made or anticipated in the protocol: Increase in number of subjects (see above) - Publications, indicating whether the GCRC was cited: None so far.

SPID:	0596	PROTOCOL:	596	TYPE:	RESEARCH	
SHORT TITLE:	Chlorhexidine and Localized Taste Stimulation					
LONG TITLE:	Effect of Chlorhexidine on Taste in Specific Regions of the Tongue in Humans					
AIDS:	N	TOTALS		A	B	D
		Inpatient		0	0	0
START DATE:	5/1/2005	Scatter Bed		0	0	0
Total # pts expected for entire study:	24	Outpatient		10	0	0
		Scatter RN Hours		0	0	0
		Offsite Visits		1	0	0
RESEARCH BIONUTRITION	N	MULTICENTER STUDY		N		
INFORMATICS CORE	Y	CLINICAL TRIAL		N		
BIostatistician	N	CORE LAB		N		
ANCILLARIES ONLY	N					

INVESTIGATOR	DEPARTMENT	NON-HOST INSTITUTION: STATE, COUNTRY
FRANK, MARION E DMD	ORAL DIAGNOSIS	
FORMAKER, BRADLEY PHD	Oral Health & Diagnostics	
HETTINGER, THOMAS PHD	Oral Health & Diagnostic	
MARKS, LAWRENCE E PHD	GENERAL MEDICINE	PIERCE FOUNDATION LABORATORY, CT USA

SUBPROJECT DESCRIPTION:

The effect of chlorhexidine on taste perception with whole-mouth stimulation is well established. The intensities of both salty and bitter compounds are reduced after treatment with chlorhexidine, the active ingredient in mouth rinses used to control periodontitis. This study addresses whether effects on salty and bitter are localized to distinct regions of the human tongue. The hypothesis is that salty will be affected more on the front of the tongue, bitter on the back of the tongue. The hypothesis is based on differential localization of specific taste qualities to distinct areas. For example, salt receptors are differentially located to the front of the tongue; whereas, bitter receptors are located more to the back of the tongue. Subjects, who will be tested for taster status with 6-n-propylthiouracil, will be 24 paid volunteers. Treatment rinses include 1.34 mM chlorhexidine gluconate, the concentration in Peridex[®], and a water control. Test stimuli are: 1.0 M NaCl, 32 mM citric acid, 1.0 M sucrose and 1.0 mM quinine. Subjects will participate in 2 sessions, with one rinse condition per session (1.34 mM chlorhexidine or water) and at least 2 days between sessions. Rinse condition for sessions will be randomly assigned. Following a 5-min waiting period after the treatment rinse, stimuli will be applied with a cotton swab to 8 points on the tongue: The tip, lateral edge, dorsal rear and palate, bilaterally; exactly as presented in the Taste and Smell Clinic Spatial Taste Test. Bilateral test stimuli will be presented at a pace of 1 per min. The effect of chlorhexidine on different tongue regions will be analyzed using repeated measures ANOVA. Within subjects factors include time (before and after treatment rinse), chlorhexidine concentration (0, 1.34 mM), and stimulus compound (NaCl, citric acid, sucrose, quinine). Our predicted outcome is that chlorhexidine effects on bitter taste will be more substantial on the tongue's lateral edge and dorsal rear sites than on the tongue tip and palate. The chlorhexidine effects on the salty taste will be the opposite: more substantial on tongue tip and palate than on lateral edge and dorsal rear tongue sites. An alternate outcome is that effects on salty and bitter tastes will be similar in all regions

SUBPROJECT PROGRESS:

Twelve subjects have been tested in our first study. Twelve additional subjects were tested to estimate equally intense sensations for a series of salts for a preliminary study. We have no unexpected safety concerns. We have no proposed changes made or anticipated in this protocol. At this time we have completed one study. Results are summarized below. Taste Intensity and Quality Identification in CN VII & CN IX Oral Sites, Effects of CHX Rinse: Three-minute CHX rinses reversibly reduce whole-mouth intensity ratings for NaCl and quinine?HCl, not sucrose or citric acid (Frank et al., 2001). Using the UConn Taste and Smell Clinics spatial test, 12 subjects (8 tasters, 4 non-tasters of n-propylthiouracil (PROP)) rated the intensity and identified the taste quality of sweet sucrose, salty NaCl, sour citric acid, and bitter quinine?HCl. The stimuli were applied with cotton swabs to regions where taste-buds innervated by the chorda tympani (fungiform & palate, CN VII) or glossopharyngeal (foliate & circumvallate, CN IX) are located. As with whole mouth testing, CHX-induced reductions were specific to NaCl and quinine. However, the pattern of intensity reduction with CHX rinse across taste-bud fields differed for NaCl and quinine (p = .001). Regardless of PROP status, the bitterness elicited by quinine was stronger in posterior than anterior taste-bud fields, but CHX reduced responses in the two fields by similar amounts.

However, although saltiness elicited by NaCl was equally intense in anterior and posterior fields, CHX rinses reduced NaCl responses more in anterior regions. This result is reminiscent of distinctions shown in responses to NaCl by rodent taste-nerves during amiloride-inhibition [Formaker & Hill, 1988; 1991]. NaCl responses in the CT field contain amiloride-sensitive and amiloride-insensitive components; whereas, the GL field is amiloride-insensitive. Thus, it is possible that the taste of salt has two mechanistic components, one more and one less inhibited by CHX. This work was submitted for fulfillment of a Master's degree in Neuroscience at the University of Hartford, which was granted.

SPID:	0597	PROTOCOL:	597	TYPE:	RESEARCH	
SHORT TITLE:	Geriatric Trauma: Tibial Shaft Fracture Study					
LONG TITLE:	Geriatric Trauma: Tibial Shaft Fracture Study					
AIDS:	N	TOTALS		A	B	D
		Inpatient		0	0	0
START DATE:	7/21/2005	Scatter Bed		0	0	0
Total # pts expected for entire study:	100	Outpatient		0	0	0
		Scatter RN Hours		0	0	0
		Offsite Visits		0	0	0

RESEARCH BIONUTRITION	N	MULTICENTER STUDY	N
INFORMATICS CORE	Y	CLINICAL TRIAL	N
BIostatistician	Y	CORE LAB	N
ANCILLARIES ONLY	N		

INVESTIGATOR	DEPARTMENT	NON-HOST INSTITUTION: STATE, COUNTRY
PERDRIZET, GEORGE MD, PHD	TRAUMA	HARTFORD HOSPITAL, CT USA

SUBPROJECT DESCRIPTION:

Population demographics tell us that the older age group (65 years of age and older) is the fastest growing segment of the US population today. Care of the elderly trauma patient demands significantly more resources than their younger counterparts. Recent advances in geriatric medicine and the basic sciences must be understood and applied to the older trauma patient if we wish to maximize patient outcomes. We have established a Geriatric Trauma Working Group, based on collaboration between clinicians and basic scientists in medicine and surgery, to study aspects of injury and recovery that will lead to improved, state of the art, care for geriatric trauma patients treated at Hartford Hospital.

Timely and complete fracture healing is important for patient rehabilitation and restoration of quality of life, particularly for older persons. The healing of tibial shaft fractures is a good model to study, as it is a common clinical problem due to trauma at all ages.

The immediate objectives of the proposed study are two fold:

1. determine if age is an independent predictor of the time to fracture healing; and
2. determine if markers of bone metabolism, either alone or in combination with patient demographic and health factors, can be used for the early identification of patients at risk for poor bone healing. If such a subset of patients can be identified then they can be targeted for early interventional therapies designed to aid the bone healing process. If we are successful then randomized, prospective interventional trials can be initiated, driven by hypotheses based on the combined knowledge base provided by members of the Geriatric Trauma Working Group.

SUBPROJECT PROGRESS:

No subjects have been enrolled during the last reporting period. Due to the fact that we had a very hard time enrolling from the oldest age group, and due to funding issues, we are considering terminating this project with the Hartford Hospital Institutional Review Board (IRB). We have not yet reached a decision on this as we may still ask a radiology student or resident to help review the radiology outcomes on patients previously enrolled.

SPID: 0598	PROTOCOL: 598	TYPE: RESEARCH
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SHORT TITLE:	DPH Project 1
LONG TITLE:	Cigarette Smoking and Effects on Infant/Child Health (Project 1)

AIDS:	N	TOTALS	A	B	D
		Inpatient	0	0	0
START DATE:	8/18/2005	Scatter Bed	0	0	0
Total # pts expected for entire study:	30	Outpatient	0	0	0
		Scatter RN Hours	0	0	0
		Offsite Visits	0	0	0

RESEARCH BIONUTRITION	N	MULTICENTER STUDY	N
INFORMATICS CORE	Y	CLINICAL TRIAL	N
BIostatistician	N	CORE LAB	N
ANCILLARIES ONLY	N		

INVESTIGATOR	DEPARTMENT	NON-HOST INSTITUTION: STATE, COUNTRY
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ONCKEN, CHERYL MD	Medicine	
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SUBPROJECT DESCRIPTION:

Cigarette smoking is responsible for the greatest number of preventable poor outcomes among pregnant women. How tobacco smoke harms developing fetuses is largely unknown. We propose to explore mechanisms that may explain how maternal tobacco use leads to low birth weight among infants. This translational tobacco research project focuses on identifying new biomarkers of prenatal tobacco exposure, which is important to understanding the effects of maternal smoking on infants and children. Project 1 hypothesizes that tobacco smoke changes the chemical structure of genes in the placenta (i.e., DNA methylation) and in the baby critical to fetal growth by altering Deoxyribonucleic acid (DNA) methylation. The ultimate effect of these changes may be low birth weight. Cord and placental tissue will be obtained at the time of delivery from 15 smokers and from 15 nonsmokers. Many of these samples will be obtained from subjects who are already participating in R01 "Nicotine Replacement Treatment for Pregnant Smokers" that is being conducted at Hartford Hospital.

Maternal DNA will be extracted using our standard techniques. The DNA will be subjected to sodium bisulfite treatment that converts unmethylated but not methylated cytidine to uracil. Sodium bisulfite treatment will be performed using standard protocols. Ribonucleic acid (RNA) from umbilical cord, placenta, and maternal blood will be extracted utilizing Trizol protocol. Measurement of Insulin-like growth factor 2 (IGF2) Messenger Ribonucleic Acid (mRNA) levels will be performed by standard quantitative real-time polymerase chain reaction (RT-PCR) techniques.

SUBPROJECT PROGRESS:

We have enrolled 15 smokers and non-smokers to examine methylation of IGF2 gene in cord tissue. Of these subjects, IGF2 analyses has been completed on everybody. During the next few months, we propose to complete the analyses for all subjects and analyze the data, and generate a report for publication. We have completed the microarray analyses of the cord and placental tissue on 15 smokers and 15 never smokers. We are writing the paper and it will go out in 2 months. And finally, the data analyses is also underway. We hope to have this completed by August of 2007. Thus, all subjects have been enrolled. We are currently analyzing the samples and hope to report the data in a manuscript in the coming year.

SPID: 0599 **PROTOCOL:** 599 **TYPE:** RESEARCH

SHORT TITLE: Genetics of Relapse Risk
LONG TITLE: Genetic Versus Phenotypic Markers of Relapse Risk

AIDS:	N	TOTALS	A	B	D
		Inpatient	0	0	0
START DATE:	8/18/2005	Scatter Bed	0	0	0
Total # pts expected for entire study:	250	Outpatient	82	0	0
		Scatter RN Hours	0	0	0
		Offsite Visits	0	0	0

RESEARCH BIONUTRITION	N	MULTICENTER STUDY	N
INFORMATICS CORE	N	CLINICAL TRIAL	N
BIostatistician	Y	CORE LAB	Y
ANCILLARIES ONLY	N		

INVESTIGATOR	DEPARTMENT	NON-HOST INSTITUTION: STATE, COUNTRY
BAUER, LANCE D PHD	PSYCHIATRY	
COVAULT, JONATHAN MD, PHD	Psychiatry	
GELERNTER, JOEL E MD	PSYCHIATRY	YALE UNIVERSITY, CT USA

SUBPROJECT DESCRIPTION:

The general goal of the proposed work is to test a theory that links the Catechol-O-methyl transferase (COMT) and gamma-aminobutyric acid A receptor, alpha 2 (GABRA2) genes to intermediate phenotypes, and, in turn, to the important clinical problem of relapse to substance abuse. It will test whether genes that have been empirically linked to substance dependence, and to measures of frontal brain function (viz., fast b power in the spontaneous electroencephalogram and frontal P300a amplitude), also confer an increased risk for relapse to these disorders. The specific goals of the project are: (1) to examine whether the genotypes of 100 cocaine-, heroin, or polydrug-dependent patients who return to substance use within 4 months after study enrollment are different from those of 100 patients who successfully maintain abstinence and 50 non-substance-dependent controls; (2) to replicate our previous findings of enhanced electroencephalographic (EEG) fast b activity and reduced frontal P300a amplitude in patients who return to substance use in comparison to patients who maintain abstinence and to healthy non-substance-dependent controls; (3) to determine if polymorphisms in GABRA2 and COMT genes are respectively associated with phenotypic variation in EEG fast b power and frontal P300a amplitude; (4) to determine if genetic markers improve the prediction of relapse beyond the predictive accuracy attained with EEG fast b power and frontal P300a amplitude, in combination with other known risk factors, including severity/chronicity of dependence, age, type of substance dependence, and Antisocial Personality Disorder.

SUBPROJECT PROGRESS:

This report describes progress during Year 2 of NIDA grant # R01 DA017666-01A2 and GCRC #599, "Genetic versus phenotypic markers of relapse risk". As of March 19, 2007, we have successfully recruited and tested 53 patients. The current pace of recruitment is consistent with the 0.75 patients per week accrual rate (18 months to date x 4 weeks per month x 0.75 pts/week = 54 pts) specified in the grant proposal. Because of the equipment difficulties during the initial months of the award (which were resolved), the number of patients recruited to date had lagged behind our projection. To resolve the minor shortage, we increased the accrual rate to 2 patients per week over the past few months and met our target. All of the proposed recruitment sites have now been accessed. Therefore, we anticipate no difficulties in attaining the proposed recruitment goals. There have been no safety concerns. There are no anticipated changes. We hope to begin preliminary analyses of the data during Year 3 and prepare the results for publications.

SPID: 0600 **PROTOCOL:** 600 **TYPE:** RESEARCH

SHORT TITLE: DPH Project 2

LONG TITLE: Impact of Maternal Smoking on Auditory Behavior in Infants and Nicotinic Cholinergic Receptor Activation

AIDS:	N	TOTALS	A	B	D
		Inpatient	0	0	0
START DATE:	10/13/2005	Scatter Bed	0	0	0
Total # pts expected for entire study:	96	Outpatient	0	0	0
		Scatter RN Hours	11	0	0
		Offsite Visits	0	0	0

RESEARCH BIONUTRITION	N	MULTICENTER STUDY	N
INFORMATICS CORE	N	CLINICAL TRIAL	N
BIostatistician	N	CORE LAB	Y
ANCILLARIES ONLY	N		

INVESTIGATOR	DEPARTMENT	NON-HOST INSTITUTION: STATE, COUNTRY
HUSSAIN, NAVEED MD	Pediatrics	
CAPRIGLIONE, ANTOINETTE MD	OBSTETRICS/GYNECOLOGY	NEW BRITAIN GENERAL HOSPITAL, CT USA
TURNER, GARY MD	OBSTETRICS/GYNECOLOGY	NEW BRITAIN GENERAL HOSPITAL, CT USA
WEINER, SCOTT MD	PEDIATRICS	NEW BRITAIN GENERAL HOSPITAL, CT USA

SUBPROJECT DESCRIPTION:

Tobacco smoke contains over 4000 chemicals and 60 carcinogens, thus the mechanisms by which maternal smoking causes fetal and infant harm are likely to be multi-factorial. Studies suggest that infants born to smokers have altered auditory processing, which has been correlated with deficits in reading and spelling in school-aged children. Nicotine exerts its effects mostly via specific receptors in both neuronal and non-neuronal tissue which may, in turn modulate expression of cytokines, which act as mediators. However the roles played by nicotinic receptors and cytokines in fetal development have not been well studied. Objective: 1. To determine if maternal smoking during pregnancy is associated with infant abnormalities in the auditory component of the Brazelton Neonatal Behavioral Assessment Scale (BNBAS), a scale devised to test auditory function. 2. To determine if maternal smoking increases/alters nicotinic receptor (nAChR) expression in umbilical cord blood and cord tissue, a non-neuronal tissue that is more readily available. 3. To determine if maternal smoking causes an increased level of the inflammatory cytokine interleukin-8 (IL-8) in fetal circulation, which in turn may be related to neuronal injury and auditory dysfunction in infants and in turn will serve as a potential biomarker to predict which babies are at risk. 4. Differences in nAChR expression and IL-8 production will be correlated with auditory functioning in newborn infants of smokers and non-smokers.

SUBPROJECT PROGRESS:

77 mothers were recruited, of which 44% were smokers (S) and 56% were non-smokers (NS). There was no difference in groups with regards to ethnicity, race and sex of the baby but a difference was noted with respect to maternal age (less in smokers - $P=0.02$). The birth weight (BW) of babies in the S group (2.48 kg 0.40) was < the NS group (3.31 kg 0.40); $p < 0.0001$. IL8 protein in cord blood/tissue was higher in S (125.03) vs NS (43.12) (F statistic = 0.0006) which correlated with poor scores on the NBAS exam $p < 0.05$. On logistic regression using NBAS scores and smoking status, controlling for birth weight, babies in the S group had poor scores with regards to habituation items, with a worse performance in inanimate and animate auditory and visual (social-interactive) items. Quality of alertness was poor in babies of S group, $p = 0.01$. Conclusions: The birth weight of babies born to smokers was < that of non-smokers. The babies of mothers who smoked were found to have poor scores on the auditory and visual components of the NBAS exam which when combined with high IL8 levels may help in identifying babies with neurodevelopmental problems in the newborn period. Abstract presented at the Society for Pediatric Research Meeting in Toronto Canada, May 6, 2007.

SPID: 0601	PROTOCOL: 601	TYPE: RESEARCH
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SHORT TITLE: TRH Administration for Fatigue
LONG TITLE: A Pilot, Randomized Double-Blind Placebo-Controlled Crossover Study of Synthetic Thyrotropin Releasing Hormone (TRH) Administration for the Treatment of Fatigue in Patients with Breast or Prostate Cancer

AIDS:	N	TOTALS	A	B	D
		Inpatient	0	0	0
START DATE:	8/18/2005	Scatter Bed	0	0	0
Total # pts expected for entire study:	48	Outpatient	9	0	0
		Scatter RN Hours	0	0	0
		Offsite Visits	0	0	0

RESEARCH BIONUTRITION	N	MULTICENTER STUDY	N
INFORMATICS CORE	N	CLINICAL TRIAL	N
BIostatistician	N	CORE LAB	Y
ANCILLARIES ONLY	N		

INVESTIGATOR	DEPARTMENT	NON-HOST INSTITUTION: STATE, COUNTRY
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WINOKUR, ANDREW MD	Psychiatry	
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SUBPROJECT DESCRIPTION:

Fatigue is the most common and the most debilitating symptom of cancer and cancer treatments. In at least 50% of cancer patients, the etiology of fatigue remains unidentified even after a comprehensive work-up. This idiopathic' cancer fatigue (iCF) is highly prevalent in patients with breast cancer and prostate cancer. Despite its high prevalence and its devastating effect on quality of life, very little evidence exists on pharmacological interventions for treatment of this incapacitating problem affecting the lives of millions of cancer patients. Until we identify the precise mechanisms underlying the pathophysiology of cancer fatigue, it is crucial that we evaluate and develop novel pharmacological interventions targeting the general hypoarousal mechanisms. The analeptic properties of thyrotropin-releasing hormone (TRH) are well established in multiple animal models. Intravenous TRH studies conducted in patients as a cognitive enhancer and an antidepressant, confirmed these analeptic actions of TRH. Patients in these trials showed significant and persistent improvement in energy, motivation, cognition and psychomotor retardation. This novel pilot study proposes a 4-week randomized double blind placebo-controlled cross-over trial to evaluate the efficacy and safety of synthetic thyrotropin-releasing hormone (TRH) to treat cancer-related fatigue in breast cancer and prostate cancer patients. In addition to assessing the impact of TRH administration on fatigue, we will also investigate its impact on patients' depressive and anxiety symptoms, overall psychological status, overall quality of life and global clinical status. We will also investigate the impact of TRH administration on immune and endocrine dysfunction associated with the cancer-related fatigue. This pilot study is a proof-of-principle study and is a vital first step towards the future development of TRH-based therapeutics including oral TRH analogs to treat cancer-related fatigue.

SUBPROJECT PROGRESS:

Number of subjects enrolled during the report and since initiation of the study: 1 Recruitment: No changes in total number of subjects we plan to recruit. We are planning to expand our recruitment efforts to Hartford Hospital and have received University of Connecticut Health Center (UCHC) Institutional Review Board (IRB) approval for specific advertisement material for Hartford hospital. We have also received approval from Hartford hospital IRB for this recruitment effort. Unexpected safety concerns and their resolution: None to report No data or outcomes to report as the collected data remains blinded at present time No proposed or anticipated changes to the protocol. Changes in coinvestigators and compensation amount per study session approved by IRB. General Clinical Research Center (GCRC) staff has been updated about these changes. No publications to report at present time.

SPID: 0602	PROTOCOL: 602	TYPE: RESEARCH
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SHORT TITLE: Asthmaticus

LONG TITLE: β -Adrenergic Receptor Polymorphisms: Implications for the Treatment of Status Asthmaticus in Children

AIDS:	N	TOTALS	A	B	D
		Inpatient	0	0	0
START DATE:	11/17/2005	Scatter Bed	0	0	0
Total # pts expected for entire study:	90	Outpatient	0	0	0
		Scatter RN Hours	34	0	0
		Offsite Visits	0	0	0

RESEARCH BIONUTRITION	N	MULTICENTER STUDY	N
INFORMATICS CORE	N	CLINICAL TRIAL	N
BIostatistician	N	CORE LAB	Y
ANCILLARIES ONLY	N		

INVESTIGATOR	DEPARTMENT	NON-HOST INSTITUTION: STATE, COUNTRY
CARROLL, CHRISTOPHER MD	PEDIATRICS	CONNECTICUT CHILDREN'S MEDICAL, CT USA
SCHRAMM, CRAIG MD	Pediatric Pulmonary	
ZUCKER, AARON MD	PEDIATRICS	CONNECTICUT CHILDREN'S MEDICAL, CT USA

SUBPROJECT DESCRIPTION:

Receptor agonists are the most important group of drugs used in the treatment of asthma. A number of studies have established that genetic variations of the β 2-adrenergic receptor have important effects in modulating responses to therapy for asthma. We propose to investigate the influence of a patient's β 2-adrenergic receptor genotype on the clinical response to β 2-AR agonist therapy during acute severe asthma exacerbation in children.

The overall objective is to assess the influence of a patient's β 2-adrenergic receptor (β 2-AR) genotype on the clinical response to β 2-AR agonist therapy. Our hypothesis is that children admitted with status asthmaticus who are homozygous for the Gly16 allele of the β 2-AR gene have a longer Intensive Care Unit (ICU) length of stays than children who are heterozygous at this locus or homozygous for the Arg16 allele when treated with high-dose continuous β 2-AR agonists (both inhaled and intravenous). Secondary aims are (1) to assess the rate of improvement in MPIS based on genotype and (2) to attempt to correlate asthma phenotype with genotype by comparing demographic data and hospital course.

SUBPROJECT PROGRESS:

β 2-adrenergic receptor (β 2-AR) agonists are the most important group of drugs used in the treatment of asthma. In children unresponsive to inhaled β 2-AR agonist therapy, higher dose systemic β 2-AR agonist therapy is frequently the next step in treatment. Despite the widespread use of intravenous β 2-AR agonist therapy for pediatric status asthmaticus, there is controversy regarding the efficacy of this therapy. We believe that genotypic differences may contribute to poor or adverse response to acute β 2-AR agonist treatment. Our specific hypothesis is that children homozygous for the Gly16 allele of the gene encoding the β 2-AR will have an altered response to acute high-dose continuous β 2-AR agonist therapy (both inhaled and intravenous) compared to children who are heterozygous at this locus or who are homozygous for the Arg16 allele. There are two arms to this trial, a prospective arm and a retrospective arm. The retrospective arm to this trial was added by IRB addendum on February 28, 2006 and this change was approved by Dr. Hesselbrock on March 30th, 2006. Currently 45 children have enrolled in the prospective arm and 32 children have enrolled in the retrospective arm. The core laboratory at the GCRC has successfully able to obtain genotype results on all patients enrolled in the study. In the prospective arm, children are prospectively enrolled on admission to the ICU with a diagnosis of status asthmaticus. We plan to enroll 90 children over a 2 year period in this arm of the trial. Enrollment in this arm began on December 28th, 2005. As of the end of January, 2007, thirteen months since the prospective arm began, 48 children meeting the inclusion criteria have been admitted to the ICU. Forty-five of these consented and were enrolled in this study. This puts us on schedule to complete enrollment very close to the 2 year timetable. In the retrospective arm of this trial, children admitted to the ICU for status asthmaticus between 2002-2005 were contacted for genetic samples obtained via saliva. Children hospitalized during this period were treated with a protocol that titrated β 2-AR therapy (first nebulized, then intravenous) according to clinical asthma score. The charts of those who provided samples were retrospectively reviewed. Genotyping of the β 2-AR gene at amino acid position 16 and 27 was performed by restriction fragment length polymorphism at the core laboratory of the GCRC under the direction of Dr. Jonathan Covault.

Thirty-two children hospitalized in the ICU during the study period consented to enrollment. At amino acid position 16, thirteen children were homozygous for the Gly16 allele (Gly/Gly), seven children were homozygous for the Arg16 allele (Arg/Arg), and 12 children were heterozygous (Arg/Gly). Despite similar clinical asthma scores on admission, children with the Gly/Gly genotype had significantly shorter ICU length of stay (43 +/- 25 vs. 76 +/- 37 hours; $p=0.01$), duration of continuous albuterol therapy (3.0 +/- 0.9 vs. 5.2 +/- 2.0 days; $p=0.002$), and were significantly less likely to require IV β 2-AR therapy (31% vs. 74%; $p=0.02$). There was no association between polymorphisms at amino acid position 27 (Glu27Gln) and response to β 2-AR therapy during acute exacerbations. Haplotype analysis was also not significant. Statistical analysis was performed by Steve Walsh at the Center for Biostatistics at UCHC. From this data, we concluded that a child's β 2-AR genotype significantly affected that child's response to acute β 2-AR agonist therapy. The clinical implication is that knowledge of a child's genotype could significantly impact treatment received for severe asthma exacerbations. An abstract summarizing these findings has been submitted to the American College of Chest Physicians International Meeting for presentation in October 2007 (pending acceptance). Support and funding from the GCRC has been cited in this abstract. There have been no safety concerns or adverse events associated with this study. There are no proposed changes to this study. Other than the abstract submitted above, there have been no associated publications.

SPID: 0604 **PROTOCOL:** 604 **TYPE:** RESEARCH

SHORT TITLE: Mental Illness

LONG TITLE: Trauma and Severe Mental Illness: Coping Skills and Stress Reduction Techniques

AIDS:	N	TOTALS	A	B	D
		Inpatient	0	0	0
START DATE:	11/17/2005	Scatter Bed	0	0	0
Total # pts expected for entire study:	60	Outpatient	0	0	0
		Scatter RN Hours	0	0	0
		Offsite Visits	0	0	0

RESEARCH BIONUTRITION	N	MULTICENTER STUDY	N
INFORMATICS CORE	Y	CLINICAL TRIAL	N
BIostatistician	N	CORE LAB	N
ANCILLARIES ONLY	N		

INVESTIGATOR	DEPARTMENT	NON-HOST INSTITUTION: STATE, COUNTRY
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FORD, JULIAN D PHD	PSYCHIATRY	
ALBERT, DAVID PHD	Psychiatry	
TENNEN, HOWARD PHD	Community Medicine	

SUBPROJECT DESCRIPTION:

The study of adults with serious mental illness will evaluate two promising manualized therapeutic interventions for complex post-traumatic stress disorder (PTSD): 1) Trauma Adaptive Recovery Group Education and Therapy (TARGET) and Present-Centered Therapy (PCT), as proposed in the Principal Investigator's (PI's) National Institute of Mental Health (NIMH) Career Development study grant. Both interventions will provide 16 one-to-one educational and therapeutic sessions that teach coping skills and stress reduction techniques.

The aims of the study are: Aim 1) To test how participation in TARGET and PCT relates to clinically and statistically significant improvements will occur in PTSD symptoms, psychosocial functioning, and emotion/impulse regulation; Aim 2) To compare the differential affects of TARGET and PCT on affect regulation, social support, stress-related information processing and cognitive coping, and the reduction of serious mental illness (SMI) symptoms; Aim 3) To identify changes in daily self-regulation after TARGET and PCT.

A diverse sample (N=60) of adults will be recruited in the UConn Department of Psychiatry Partial Hospital Program (PHP) and offered the opportunity to receive 16 sessions of individualized counseling when they are discharged from PHP. After screening for eligibility and obtaining valid signed consent forms, participants will be randomly assigned to one of the two experimental conditions. Psychometric self-report and daily monitoring measures will be obtained at baseline, post-treatment, and 4-month follow-up assessments and multivariate statistical techniques will be used for analysis of treatment effects.

The study builds on findings by the PI and Co-I Albert who have demonstrated that adults with SMI commonly have untreated PTSD.

SUBPROJECT PROGRESS:

13 participants have been recruited between 4/21/06 and 3/31/07. A total of 18 participants have been recruited in the study. The following changes have been made to the study since last April:

- A new measure was added. Clinical Outcomes in Routine Evaluation Outcome Measure (CORE-OM) (Barkham, Margison, Leach, Lucock, Mellor-Clark, et al., 2001; Evans et al., 2002) is a 34-item outcome measure that reliably assesses 4 domains/constructs: subjective well being (4 items), psychiatric symptoms of anxiety (4 items), depression (4 items), physical symptoms (2 items), trauma (2 items), social functioning (12 items), and risk assessment of harm to self or others (6 items). This assessment has been designed and validated to compare psychological therapy outcomes across different clinical settings providing usual care with controlled clinical trials.

- We added a treatment as usual group (TAU) control group. In consultation with the PHP/IOP clinicians and administration, we determined that offering the primary treatment (TARGET or MET-CBT) at a delay of either 8 or 16 weeks will pose no added risk to

participants and will provide a scientifically-sound comparison for a re-submission if the proposal to NIH based on testing the benefits of providing TARGET or MET-CBT at three timepoints, i.e., immediately, two months, and four months after PHP/IOP discharge. TAU typically consists of outpatient medication management, case management, psychotherapy sessions, support groups, relapse prevention groups, and 12-step (addiction recovery) groups. In order to address reviewer concerns about counselor contact alone resulting in benefit, we added a PTSD Education/Enhanced TAU condition (PTAU), which offers the same number of contacts on an identical schedule (twice weekly for 6 weeks, and 2 additional counseling sessions, once per month) to that received by TARGET and MET-CBT. PTAU will provide education about disease management and coping with PTSD, which is derived from well-established protocols developed by the study's expert consultant, Dr. Kim Mueser. The study hypothesis is that the TARGET or MET-CBT will provide additional benefits beyond those of TAU or PTAU in terms of symptom reduction and stable functioning.

- A Data Safety Monitoring Board (DSMB) was formed, with Drs. Josephine Hawke, Geraldine Pearson, and Andrew Winokur serving as DSMB members.

- Monetary incentives were added for Interactive Voice Response (IVR) completion. We increased the incentives by offering participants a dollar a day for each of the 21 days they call in on the IVR system.

Preliminary outcomes: Of the first eight participants (6 female, 2 male), all met Structured Clinical Interview for DSM-IV-TR (SCID) criteria for either schizoaffective, bipolar, major depressive, or obsessive compulsive disorder. Three participants have completed the 6-week 12-session TARGET intervention, and five others are enrolled and are completing either TARGET or a MET-based comparison treatment, with no attrition to date. Among the three participants who have completed the treatment, TARGET is associated with of clinically significant change and medium to large effect sizes in interpersonal functioning (IIP-32: Baseline M(SD) = 55.0 (23.8), Post-test M(SD) = 31.3(15.9), $\eta^2=.50$), CAPS PTSD symptoms (Baseline M(SD) = 94.6(43.5), Post-test M(SD) = 46.0(22.5), $\eta^2=.83$) and BPRS (Baseline M(SD) = 46.0(3.5), Post-test M(SD) = 35.3(4.7), $\eta^2=.99$).

SPID: 0605 **PROTOCOL:** 605 **TYPE:** RESEARCH

SHORT TITLE: Alcohol and HIV+

LONG TITLE: Alcohol-involved Sexual Risk Behavior Among HIV Positive Persons

AIDS:	Y	TOTALS	A	B	D
		Inpatient	0	0	0
START DATE:	1/1/2006	Scatter Bed	0	0	0
Total # pts expected for entire study:	215	Outpatient	0	0	0
		Scatter RN Hours	0	0	0
		Offsite Visits	0	0	0

RESEARCH BIONUTRITION	N	MULTICENTER STUDY	N
INFORMATICS CORE	Y	CLINICAL TRIAL	N
BIostatistician	N	CORE LAB	N
ANCILLARIES ONLY	N		

INVESTIGATOR	DEPARTMENT	NON-HOST INSTITUTION: STATE, COUNTRY
BARTA, WILLIAM D PHD	PSYCHOLOGY	UCONN - STORRS, CT USA
ABU-HASABALLAH, KHAMIS PHD	Psychiatry	
TENNEN, HOWARD PHD	Community Medicine	

SUBPROJECT DESCRIPTION:

The proposal examines the relationship between prior alcohol use and sexual risk-taking among economically disadvantaged people living with Human Immunodeficiency Virus/Acquired immune deficiency syndrome (PLWHA). Empirical data regarding the hypothesized relationship between prior alcohol use and sexual risk-taking has been inconsistent. This proposal seeks to (1) apply a daily process research methodology (Tennen et al., 2000) to this empirical question, in order to overcome some of the limitations of past research, and (2) evaluate the hypothesis that the relationship between alcohol use and sexual risk behavior is moderated by the effect of disinhibiting emotional states (such as those generated by situational exposure to affect-charged daily events or "affective events") on social-cognitive predictors of sexual risk reduction (such as condom use-related self-efficacy and attitudes). The latter objective is based on the premise that being HIV seropositive and facing the chronic stressors associated with economic disadvantage imposes profound chronic stress; chronic stress, in turn, increases vulnerability to high emotional reactivity when confronting acute stressors (McEwen, 2001). From the perspective of Self-Regulation Theory (Baumeister, 1997; Hull & Slone, 2004), individuals experiencing high emotional reactivity are susceptible to situational lapses in subjective self-control; however, this theory has not been applied in a systematic manner to daily variations in condom use and abstinence behaviors among disadvantaged PLWHA. The daily process methodology involves collecting within- and between-person data; within-person data will be collected on a "near time", in vivo basis using a daily survey administered via a telephone-based Interactive Voice Response (IVR) technology. The daily survey will continue over a period of 6 weeks and involve a total of 215 PLWHA. Alcohol-related and sex-related events will be recorded, along with affective events, to test the study hypotheses.

SUBPROJECT PROGRESS:

Since the previous annual report additional participants have been enrolled in a 5-week diary study, bringing the total to 199 completed diaries. After discussion with National Institute of Alcohol Abuse and Alcoholism (NIAAA), this recruitment number is close enough to the goal of 215 that the aims of the research are likely to be achieved, and recruitment has ended. No adverse events have been reported. The first manuscript associated with these data is in its final preparation stages.

SPID: 0606	PROTOCOL: 606	TYPE: RESEARCH
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SHORT TITLE:	Bariatric
LONG TITLE:	Ventilatory Dysfunction in Eucapnic and Hypercapnic Obese Subjects Pilot

	AIDS:	N	TOTALS			
				A	B	D
			Inpatient	0	0	0
START DATE:	12/27/2005		Scatter Bed	0	0	0
Total # pts expected for entire study:		30	Outpatient	3	0	0
			Scatter RN Hours	0	0	0
			Offsite Visits	0	0	0

RESEARCH BIONUTRITION	N	MULTICENTER STUDY	N
INFORMATICS CORE	N	CLINICAL TRIAL	N
BIostatistician	N	CORE LAB	Y
ANCILLARIES ONLY	N		

INVESTIGATOR	DEPARTMENT	NON-HOST INSTITUTION: STATE, COUNTRY
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BANDYOPADHYAY, TAPAS MD	Pulmonary/Medicine	
BURKI, NAUSERWAN K MD	Medicine/Pulmonary Medicin	
WATSON, KEVIN MD	Pulmonary/Medicine	

SUBPROJECT DESCRIPTION:

The incidence of obesity continues to increase. Obese subjects have complex abnormalities of the respiratory system

- 1). A minority of morbidly obese subjects are hypercapnic. Such subjects are termed as suffering from the obesity hypoventilation syndrome or the Pickwickian Syndrome. Most of these subjects tend to suffer from obstructive sleep apnea and have a higher incidence of respiratory complications. By definition, this subset of patients has chronic hypoventilation and a disorder of ventilatory control
- 2). The subjects studied will serve as their own controls as we will assess their ventilatory pattern and drive after clinically significant weight loss (following Bariatric Surgery). A group of morbidly obese subjects without daytime hypercapnia will also be studied in a similar fashion to assess for differences in inflammatory markers and ventilatory control in these two groups of obese patients. Leptin is a poorly characterized mediator that has been associated with hypoventilation
- 3). C-reactive protein (CRP) and Erythrocyte Sedimentation Rate (ESR) are commonly used indices of inflammation. Procalcitonin has recently been shown to correlate with prognosis of community acquired pneumonia (CAP).

SUBPROJECT PROGRESS:

We have performed the current study in 7 obese subjects undergoing evaluation for bariatric surgery to date. 6 subjects are eucapnic and 1 is hypercapnic. There was no history of cardiopulmonary disease in any of our subjects. There were 2 eucapnic subjects for whom P 0.1 was not available. The average age was 49.6 ± 9.5 yrs, the average Bone Mass Index (BMI) was 51 ± 10 Kg/m², the average leptin was 202 ± 66 IU, the average MV was 10.1 ± 3.5 liters/min, the average P.01 was 1.17 ± 0.64 cm H₂O, the average PaCO₂ was 39.6 ± 3.4 mm Hg. The correlation between leptin and BMI was 0.685 (significance, p=0.06), the correlation between PaCO₂ and P 0.1 was 0.397 (significance, p=0.51) and the correlation between MV/P 0.1 and PaCO₂ was -0.65 (significance, p=0.23). There have been no publications from this study so far. No safety concerns identified. This study had been currently put on hold because of changes in Bariatric Surgery Program.

SPID: 0607 **PROTOCOL:** 607 **TYPE:** RESEARCH

SHORT TITLE: Finasteride
LONG TITLE: Finasteride Effects on Subjective and Physiological Response to Alcohol

AIDS:	N	TOTALS	A	B	D
			Inpatient	0	0
START DATE:	12/1/2005	Scatter Bed	0	0	0
Total # pts expected for entire study:	30	Outpatient	0	0	0
		Scatter RN Hours	0	0	0
		Offsite Visits	0	0	0

RESEARCH BIONUTRITION	N	MULTICENTER STUDY	N
INFORMATICS CORE	Y	CLINICAL TRIAL	N
BIostatistician	Y	CORE LAB	N
ANCILLARIES ONLY	N		

INVESTIGATOR	DEPARTMENT	NON-HOST INSTITUTION: STATE, COUNTRY
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KRANZLER, HENRY R MD	PSYCHIATRY	
COVAULT, JONATHAN MD, PHD	Psychiatry	

SUBPROJECT DESCRIPTION:

The GABAA receptor is an important site of action of endogenous neuroactive steroids and an important mediator for several behavioral effects of alcohol. Neuroactive steroids such as 3 α -5 α -THP (allopregnanolone), 3 β (THDOC) are potent allosteric modulators of GABAA neurotransmission. Like alcohol, these steroids have hypnotic, anticonvulsant, anxiolytic properties, and they also attenuate stress responses mediated by the hypothalamic-pituitary-adrenal (HPA) axis. Given that alcohol's behavioral effects are similar to those produced by neuroactive steroids, which directly modulate GABAA channels, several investigators have suggested that alcohol may produce many of its physiologically important effects via endogenous steroid compounds. The aim of the present double-blind, within subject, cross-over study is to examine whether finasteride modifies the behavioral and physiological effects of a moderate dose of alcohol in a group of healthy volunteers. In addition to examining subjective and physiological effects in this human laboratory experiment, we will examine changes in the peripheral levels of 5 α -reduced steroids. The hormone measures will serve to validate the efficacy of finasteride in selectively decreasing 5 α -reduced steroid synthesis, thereby making it possible to evaluate the relative importance of 5 α -reduced steroids in the reinforcing effects of alcohol. An evaluation of this hypothesis may help to elucidate the neuropsychopharmacology of alcohol and may suggest a novel approach to the pharmacotherapy of alcohol dependence.

SUBPROJECT PROGRESS:

The study is finished, but report writing is still ongoing. Number of subjects enrolled during the report period and since initiation of the study: 38 healthy subjects. Any changes in recruitment plans that might be needed: NA. Unexpected safety concerns and their resolution: NA. Interim data and outcomes if appropriate: Yes, see publications below but report writing is still ongoing. Any proposed changes made or anticipated in the protocol: NA. Publications: Pierucci-Lagha A., Covault J., Feinn R., Morrow L.A., Marx R.C.E., Shampine L.J., and Kranzler H.R. (2005) Alcohol Induces Changes in Subjective Effects and Steroid Hormone Concentrations in Humans. *Psychopharmacology (Berl)*. 2005 Dec 10;1-11. Pierucci-Lagha A, Covault J, Feinn R, Nellissery M, Hernandez-Avila C, Oncken C, Morrow A.L. and Kranzler H.R. (2005) GABRA2 Alleles Moderate the Subjective Effects of Alcohol, Which Are Attenuated by Finasteride. *Neuropsychopharmacology* 2005 Jun;30(6):1193-203.

SPID: 0608 **PROTOCOL:** 608 **TYPE:** RESEARCH

SHORT TITLE: Prenatal Tobacco Department of Public Health ((DPH) project 3)
LONG TITLE: The Influence of Prenatal Tobacco Exposure on the Quantity of Adult Stem Cells and Progenitor Cells in the Offspring of Smokers Pilot Study

AIDS:	N	TOTALS	A	B	D
		Inpatient	0	0	0
START DATE:	12/21/2005	Scatter Bed	0	0	0
Total # pts expected for entire study:	100	Outpatient	1	0	0
		Scatter RN Hours	12	0	0
		Offsite Visits	0	0	0

RESEARCH BIONUTRITION	N	MULTICENTER STUDY	N
INFORMATICS CORE	N	CLINICAL TRIAL	N
BIostatistician	Y	CORE LAB	Y
ANCILLARIES ONLY	N		

INVESTIGATOR	DEPARTMENT	NON-HOST INSTITUTION: STATE, COUNTRY
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MORRIS, BRUCE MD	Medicine/Maternal Fetal	
AGUILA, LEONARDO PHD	Medicine	
COVAULT, JONATHAN MD, PHD	Psychiatry	
HUSSAIN, NAVEED MD	Pediatrics	
LALANDE, MARC MD	Genetics & Develop Biology	
ONCKEN, CHERYL MD	Medicine	

SUBPROJECT DESCRIPTION:

The influence of prenatal factors upon stem cell development during the nine months of gestation has the potential to impact lifelong maintenance and repair. A paucity of research has been done on the influence of prenatal environmental exposures upon the quantify of adult stem cell and progenitor subpopulations.1,2 In the hematopoietic system the subpopulations are responsible for establishment and maintenance of the immune system. Studies in mice have shown that nicotine exposure alters both Hematopoietic Stem Cell (HSC) number and hematopoietic progenitor cell function3. Other work has shown an increased incidence of respiratory diseases and a difference in the T cell response in children born to smokers.4,5

This is a pilot project to study the influence of prenatal tobacco exposure on the quantity of hematopoietic stem cells and early progenitor cells in the umbilical cord blood of the offspring of smokers. Prenatal tobacco exposure may alter both the absolute number of these populations as well as the ratio of early progenitor cells to hematopoietic stem cells. Previous research has shown that the expression of early progenitor populations, specifically myeloid/Erythroid and lymphoid progenitors can reflect functional studies on these cells6,7,8,9. It is hoped that studying HSC and progenitor populations will give insight into the impact of tobacco exposure on the role of the stem cell in repair, maintenance, and prevention of childhood disease.

Umbilical cord blood will be collected from 31 singleton smokers greater than 32 weeks gestation and a control group of 31 nonsmokers. Using commercially available monoclonal antibodies directed against cell surface markers flow cytometry will be used to quantify the HSC and subpopulations of lymphoid, myeloid, and erythroid cells. This will allow us to analyze the possible influence of prenatal tobacco exposure in early hematopoiesis. In addition, we would like to establish an effect size of the influence of prenatal tobacco exposure on HSC and populations of progenitor necessary to conduct future studies examining statistical significance.

SUBPROJECT PROGRESS:

1. Our power analysis gave us a goal of 17 samples in each arm (smokers and nonsmokers). At the end of the collection process we obtained 16 smoker samples, and 23 nonsmokers 2. We stopped recruitment 3. no unexpected safety concerns have arisen 4. We have completed analysis of our samples 5. we have made no changes in the protocol 6. No publications have been created to date. Thank you. AT this time we need continued statistical assistance, which has been as issue due to limited resources. However, we anticipate no further capital requests for this study at this time.

SPID: 0609 **PROTOCOL:** 609 **TYPE:** RESEARCH

SHORT TITLE: Metformin on Cardio Markers

LONG TITLE: Effect of Metformin on Cardiovascular Markers in Obese Adolescents Pilot Study

AIDS:	N	TOTALS	A	B	D
		Inpatient	0	0	0
START DATE:	12/14/2005	Scatter Bed	0	0	0
Total # pts expected for entire study:	30	Outpatient	23	0	0
		Scatter RN Hours	0	0	0
		Offsite Visits	0	0	0

RESEARCH BIONUTRITION	N	MULTICENTER STUDY	N
INFORMATICS CORE	Y	CLINICAL TRIAL	N
BIostatistician	N	CORE LAB	N
ANCILLARIES ONLY	N		

INVESTIGATOR	DEPARTMENT	NON-HOST INSTITUTION: STATE, COUNTRY
PHULWANI, PRIYA MD	MEDICINE/ENDOCRINOLOGY	CONNECTICUT CHILDREN'S MEDICAL, CT USA
ESTRADA, ELIZABETH MD	PEDIATRICS	CONNECTICUT CHILDREN'S MEDICAL, CT USA
THOMPSON, PAUL MD	PREVENTIVE CARDIOLOGY	HARTFORD HOSPITAL, CT USA

SUBPROJECT DESCRIPTION:

Obesity has been linked to hyperinsulinemia due to insulin resistance. Insulin resistance is defined as the inability of insulin to act at the level of its target tissues. It contributes to arterial endothelial dysfunction, which in turn is a marker for impending cardiovascular disease. As the incidence of childhood obesity approaches epidemic proportions, there is a strong need to decrease their cardiovascular risk in the long term. Metformin, an oral hypoglycemic agent, decreases insulin levels while improving endothelial dysfunction and decreasing serum markers for heart disease, in obese adults.

Our hypothesis is that metformin will decrease cardiovascular risk factors in obese adolescents with hyperinsulinemia. Our specific aims are: 1) to examine the effect of metformin on the following surrogate markers of cardiovascular disease: a) Endothelial function via ultrasound to assess dilation of the brachial artery. b) Serum markers namely C-reactive protein, von Willebrands factor, fibrinogen, homocysteine and a fasting lipid profile. 2) to study the correlation of these cardiovascular markers on indices of insulin sensitivity, namely Homeostasis Model Assessment (HOMA-index) and Quantitative insulin sensitivity check (QUICKI). Our plan is to conduct a double blinded, placebo controlled trial and measure the above at baseline and at the end of sixteen weeks. We will enroll 15 adolescents in each group - metformin 850 mg twice a day and placebo. The goal is an increase in dilation of the brachial artery of 5% in the metformin group and 1% in the placebo group; using a within subject variability of 3-4%, two-tailed significance level of 0.05 and power of 80%.

SUBPROJECT PROGRESS:

Subjects enrolled during reporting period: 1. Total subjects: 44. Recruitment is completed and there were no unexpected safety concerns. We proposed the following additional labs on 2/9/07 which were approved by the GCRC: Vitamin D 25,OH and Total Calcium on the baseline and final specimens, TSH (thyroid stimulating hormone) 3rd generation on the final specimens, and a few subjects need liver function tests and a lipid panel which were not done on their baseline specimens. Once the above test results are in, data will be analyzed. Specifically, Vitamin D 25OH 73 total (2 tests each for 29 subjects + 1 test each for 15 subjects) Total Calcium 73 total (2 tests each for 29 subjects + 1 test each for 15 subjects) TSH 29 total (1 test each for 29 subjects) AST 2 total (1 test each for two subjects) ALT 1 total (1 test for one subject) Total Cholesterol 1 total (1 test for one subject) HDL 2 total (1 test each for two subjects) Triglycerides 1 total (1 test for one subject). There are no publications to date.

SPID: 0610	PROTOCOL: 610	TYPE: RESEARCH
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SHORT TITLE: Zonisamide versus Placebo

LONG TITLE: Zonisamide versus Placebo in the Treatment of Alcohol Dependence

AIDS:	N	TOTALS	A	B	D
		Inpatient	0	0	0
START DATE:	1/19/2006	Scatter Bed	0	0	0
Total # pts expected for entire study:	50	Outpatient	34	0	0
		Scatter RN Hours	0	0	0
		Offsite Visits	0	0	0

RESEARCH BIONUTRITION	N	MULTICENTER STUDY	N	
INFORMATICS CORE	Y	CLINICAL TRIAL	Y	Phase II
BIostatistician	N	CORE LAB	N	
ANCILLARIES ONLY	N			

INVESTIGATOR	DEPARTMENT	NON-HOST INSTITUTION: STATE, COUNTRY
ARIAS, ALBERT MD	Psychiatry	
COVAULT, JONATHAN MD, PHD	Psychiatry	
KRANZLER, HENRY R MD	PSYCHIATRY	
ONCKEN, CHERYL MD	Medicine	

SUBPROJECT DESCRIPTION:

This is a pilot study designed to examine the potential efficacy and tolerability of zonisamide for the treatment of alcoholism, and to compare this to topiramate, a similar medicine with demonstrated efficacy in a randomized clinical trial. Zonisamide is potentially better tolerated and easier to titrate in the outpatient setting than topiramate.

SUBPROJECT PROGRESS:

A total of 9 subjects were enrolled during the report period (a total of 9 since initiation of the study). As of 3/31/07, a total of 8 subjects had been randomized to receive treatment with either zonisamide or placebo. There are no changes needed in recruitment plans. There have been no unexpected safety concerns associated with this study. Interim outcomes data are not available at this time. There have been no publications associated with this study since data collection is ongoing. Changes made in the protocol during the report period were: 1) change of PI to Dr. Arias, 2) a Waiver of Consent for phone screening was obtained (as per IRB guidance on this issue), 3) an Alcohol Tracking Card" was added as a subject handout (to allow subjects to track drinking data during the 2-week interval between study visits) and modifications were made to the telephone script (to allow for referral of phone excludes to other active studies), 4) we removed the baseline serum ammonia level from the protocol since hyperammonemia is not associated with zonisamide (i.e., a baseline ammonia level is not clinically relevant to the study), and 5) we updated inclusion criteria to state that subjects must meet Diagnostic and Statistical Manual of Mental Disorders, 4th Edition (DSM-IV) alcohol dependence within the past month. We also added an additional inclusion criterion that subjects must have at least 2 heavy drinking days per week during the interval in-between screening and baseline. These two clarifications of the inclusion criteria will allow for better analysis of pre- versus post-treatment drinking effects and will exclude individuals who have recently stopped drinking for a period of time, since one of the aims of the study is to evaluate how the medication can help subjects who are actively drinking to reduce or stop their drinking.

SPID: 0611	PROTOCOL: 611	TYPE: RESEARCH
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SHORT TITLE: Topiramate/Smoking

LONG TITLE: Topiramate alone or in combination with the nicotine patch for smoking cessation

AIDS:	N	TOTALS	A	B	D
			Inpatient	0	0
START DATE:	1/23/2006	Scatter Bed	0	0	0
Total # pts expected for entire study:	90	Outpatient	245	0	0
		Scatter RN Hours	0	0	0
		Offsite Visits	0	0	0

RESEARCH BIONUTRITION	N	MULTICENTER STUDY	N
INFORMATICS CORE	N	CLINICAL TRIAL	N
BIostatistician	N	CORE LAB	Y
ANCILLARIES ONLY	N		

INVESTIGATOR	DEPARTMENT	NON-HOST INSTITUTION: STATE, COUNTRY
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ONCKEN, CHERYL MD	Medicine	
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SUBPROJECT DESCRIPTION:

1. To obtain pilot data on 4-week continuous quit rates associated with either 12 weeks of treatment with topiramate alone or topiramate in combination with 10 weeks of nicotine patch for smoking cessation.
2. To obtain pilot data on the effects of 12 weeks of topiramate alone or topiramate combined with 10 weeks of nicotine patch, on nicotine withdrawal symptoms, smoking satisfaction, and adverse effects during smoking cessation.
3. To obtain pilot data on weight gain over 12 weeks with either topiramate alone or topiramate in combination with the nicotine patch.

SUBPROJECT PROGRESS:

As of May 15, 2007, 42 people have been screened, 32 randomized, 18 have completed, 6 are active, and 8 have early terms. No change in recruitment plans. No unexpected safety concerns. There is no interim data analyses done yet, and we do not anticipate changes in the protocol at this time.

SPID: 0612	PROTOCOL: 612	TYPE: RESEARCH
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SHORT TITLE: Alcohol Challenge

LONG TITLE: Alcohol Effects on Subjective and Physiological Responses

AIDS:	N	TOTALS	A	B	D
		Inpatient	0	0	0
START DATE:	2/16/2006	Scatter Bed	0	0	0
Total # pts expected for entire study:	100	Outpatient	201	0	0
		Scatter RN Hours	0	0	0
		Offsite Visits	0	0	0

RESEARCH BIONUTRITION	N	MULTICENTER STUDY	N
INFORMATICS CORE	N	CLINICAL TRIAL	N
BIostatistician	N	CORE LAB	Y
ANCILLARIES ONLY	N		

INVESTIGATOR	DEPARTMENT	NON-HOST INSTITUTION: STATE, COUNTRY
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COVAULT, JONATHAN MD, PHD	Psychiatry	
ARIAS, ALBERT MD	Psychiatry	
KRANZLER, HENRY R MD	PSYCHIATRY	
ONCKEN, CHERYL MD	Medicine	
PIERUCCI, AMIRA PHD	Psychiatry	

SUBPROJECT DESCRIPTION:

Alcohol abuse and dependence are important public health problems. Inherited (i.e., genetic) risk factors are thought to be important in the development of alcohol use disorders. Recent family-based and case-control studies of genetic factors in alcohol dependence indicate that variation in the GABA-A gene, GABRA2, is associated with alcohol dependence. Our preliminary results from alcohol challenge studies in humans suggest that variation in GABRA2 also influences the subjective effects of alcohol, suggesting a potential mechanism by which the gene may influence risk of alcohol dependence. Based on these preliminary data, the aims of this study are to: 1) examine the effect of alcohol on multiple domains of the response to acute alcohol administration in 30 social drinkers and to 2) examine the moderating effect of GABRA2 genotype on these subjective measures in response to acute alcohol administration. We hypothesize that, during the ascending limb of the BrAC, the stimulating and rewarding effects of alcohol will be moderated by GABRA2 genotype, such that individuals who are homozygous for the A-allele at SNP rs279858 (an intronic marker in GABRA2) will show a greater response to the effects of alcohol than will carriers of the alcohol-dependence-associated G-allele. In contrast, other effects of alcohol, such as sedation, motor incoordination, and decreased cognitive performance (the latter two measured by static ataxia and working memory, respectively), will not be influenced by GABRA2 genotype, as these effects are more likely to involve modulation of receptors containing the GABA-A α -1 subunit. The identification of specific genetic determinants for variation in the quality or magnitude of responses to alcohol may help in our understanding of why some individuals are vulnerable to, or protected from, alcohol dependence.

SUBPROJECT PROGRESS:

A total of 65 subjects were enrolled during the report period and a total of 70 since the initiation of the study. The study continues to enroll additional participants. There have been no unexpected safety concerns associated with this study and no serious adverse events. Several protocol changes have been made during the report period. Joel Gelernter, Xingguang Luo, and Yang Bao-zhu were added as co-investigators of the study, and Dr. Jonathan Covault, previously a co-investigator has replaced Amira Pierucci-Lagha as principal investigator. Alcohol and drug abuse exclusion criteria was changed from lifetime to past year. The Body Mass Index (BMI) criteria was changed from 18.5-30 to 18.5-32.5 and a body weight limit of 225 lbs added to limit maximum dose of alcohol that could be administered under the protocol. The amount of time allocated to consume 3 alcohol beverages was increased from 30 min to 36 min. Post-drink heart rate, blood pressure and breath alcohol measurements now begin after consuming all three drinks. The source of alcohol for the study was changed from grain alcohol to quality vodka in response to participants comments about the chemical aftertaste of the grain alcohol. The Profile of Mood States (POMS) assessment was removed from the study protocol and assessment packet. Oral contraceptives are not an exclusion criteria for this study, the incorrect statement - "women will be included if they are not on oral contraceptives or any other hormones" was deleted from the protocol description. Although recruitment plans for this study did not change during the report period, we received Institutional Review Board (IRB) approval to offer to individuals who have been phone screened and determined ineligible for this study information about other currently available studies within the addictions

research clinic that they may qualify for. No publications have resulted to date from this work. GCRC support will be cited in any publications from this project.

SPID: 0613 **PROTOCOL:** 613 **TYPE:** RESEARCH

SHORT TITLE: Vouchers versus Prizes

LONG TITLE: Vouchers versus Prizes for Cocaine-Dependent Methadone Patients

AIDS:	N	TOTALS	A	B	D
		Inpatient	0	0	0
START DATE:	2/16/2006	Scatter Bed	0	0	0
Total # pts expected for entire study:	240	Outpatient	0	0	0
		Scatter RN Hours	0	0	0
		Offsite Visits	1,314	0	0

RESEARCH BIONUTRITION	N	MULTICENTER STUDY	N
INFORMATICS CORE	N	CLINICAL TRIAL	N
BIostatistician	N	CORE LAB	N
ANCILLARIES ONLY	N		

INVESTIGATOR	DEPARTMENT	NON-HOST INSTITUTION: STATE, COUNTRY
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PETRY, NANCY M PHD	PSYCHIATRY	
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ALESSI, SHELIA PHD	Psychiatry	
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SUBPROJECT DESCRIPTION:

About 40-60% of methadone maintenance patients are also cocaine dependent. Cocaine dependence is associated with significant morbidity and mortality, but few traditional therapies are efficacious in treating cocaine dependence in this difficult patient population. Contingency management (CM) strategies that provide positive incentives upon direct evidence of cocaine abstinence are promising interventions. Typically, vouchers, exchangeable for retail goods and services, are used as reinforcers. When voucher amounts range from \$1000 to \$3000 over a 12-week treatment period, CM can reduce cocaine use in methadone patients. We have data from cocaine-dependent patients treated in drug-free settings that suggest a novel reinforcement system that provides the chance to win prizes, rather than vouchers, may also be efficacious in decreasing cocaine use, at potentially lower costs. The purpose of the study is to evaluate the efficacy of voucher and prize CM in cocaine-dependent methadone patients.

Cocaine-dependent methadone patients (n=240) will be randomly assigned to one of four conditions: standard treatment, standard treatment plus usual magnitude prize CM (\$300), standard treatment plus higher magnitude prize CM (\$900), or standard treatment plus voucher CM (\$900). Urine samples will be screened 2-3 times weekly for 14 weeks, and follow-up data will be collected throughout a 12-month period. We expect that CM will decrease cocaine use relative to standard treatment, the efficacy of prize CM will be magnitude dependent, and \$900 prize CM will be more efficacious than \$900 voucher CM.

We will also examine patient characteristics and their association with treatment response. Further, we will obtain a detailed analysis of relapse following CM treatment and evaluate the cost-effectiveness of CM. In sum, this study will provide a stringent test of the relative efficacy and cost-effectiveness of voucher and prize CM, and it will address moderators of response to CM in the treatment of cocaine-dependent methadone patients.

SUBPROJECT PROGRESS:

Total Enrollment: 66 Past Year Enrollment: 53 No changes in recruitment plans are needed. · No unexpected safety concerns have occurred. · Interim data and outcomes are not available. · Changes to protocol: 1) Added to the protocol the following names of additional recruitment sites: Liberation Programs Inc. in Stamford and Bridgeport, Connecticut. 2) Updated the protocol version with the date of 11/06 in order to facilitate study administration. 3) Added to the protocol the name of a program where recruitment will occur. The new facility is the Regional Network of Programs, Inc. (CT). · No publications to date.

SPID: 0614	PROTOCOL: 614	TYPE: RESEARCH
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SHORT TITLE:	Vitamin D Deficiency
LONG TITLE:	Vitamin D deficiency in children with cerebral palsy

AIDS:	N	TOTALS	A	B	D
			Inpatient	0	0
START DATE:	3/1/2006	Scatter Bed	0	0	0
Total # pts expected for entire study:	100	Outpatient	0	0	0
		Scatter RN Hours	0	0	0
		Offsite Visits	0	0	0

RESEARCH BIONUTRITION	N	MULTICENTER STUDY	N
INFORMATICS CORE	N	CLINICAL TRIAL	N
BIostatistician	N	CORE LAB	Y
ANCILLARIES ONLY	N		

INVESTIGATOR	DEPARTMENT	NON-HOST INSTITUTION: STATE, COUNTRY
YIGIT, SEVKET MD	PEDIATRICS	CONNECTICUT CHILDREN'S MEDICAL, CT USA
KENNY, ANNE M MD	CENTER ON AGING	

SUBPROJECT DESCRIPTION:

Our main goal is to improve the skeletal health of children with cerebral palsy (CP), a population with a high lifetime risk of fractures. In this study we seek pilot funding to examine the prevalence of vitamin D (vit D) insufficiency and deficiency in children with CP in the greater Hartford area. This is a necessary step before a planned intervention trial of vit D in children with CP. Vit D sufficiency is a requirement for normal bone mineralization, and plays roles in muscle strength, regulation of cell differentiation and immune function. Consequently, it is desirable to prevent vit D insufficiency/deficiency in children in general. Children with CP may be at higher risk for vit D deficiency because of limited exposure to unfiltered sunlight, impaired nutrition because of swallowing dysfunction and use of anticonvulsants that increase vit D breakdown. In addition, vit D deficiency is more prevalent in Northern latitudes, even among healthy children. In consequence, children with CP in the greater Hartford area may be at particular risk for vit D insufficiency/deficiency. However, there are no prevalence data concerning the sufficiency of vit D stores in children with CP in our geographical area. Our anecdotal clinical experience indicates that children with CP frequently have reduced serum 25 (OH) vit D, an indicator of vit D reserves. Therefore, we hypothesize that children with CP in the Hartford area have a higher prevalence of vit D deficiency than healthy children. To test this hypothesis, we aim to measure serum 25 (OH) vit D in children with CP and their unaffected, healthy siblings living in the same household. Seasonal differences will be examined, since vit D stores tend to decrease in colder, dimmer months. We will invite children with CP who are followed at the Special Kids Support Center (SKSC) at the Connecticut Children's Medical Center (CCMC) to participate. These children are well characterized clinically, including use of anticonvulsants. Multiple clinical specialists will assess these children. Children with CP will have motor function assessment during the study visit at SKSC and a clinical nutritionist will obtain data on calcium and vit D intake. The PI will exclude primary and secondary bone diseases. Children with vit D deficiency will be treated with oral vit D. This screening study will provide pilot data for a subsequent intervention trial that aims to find the optimal dose of enteral vit D to restore normal vit D status in children with CP. Timely identification and treatment of vit D deficiency will improve bone health in these fragile individuals.

SUBPROJECT PROGRESS:

Total of 26 subjects were enrolled in the study since the initiation. There are no changes in the recruitment plan. There are no unexpected safety concerns. There is no interim data available at this point. There are no anticipated changes in the protocol. There are no publications based upon current study yet.

SPID: 0617 **PROTOCOL:** 617 **TYPE:** RESEARCH

SHORT TITLE: Weight Reduction

LONG TITLE: Prevalence and Predictors of Weight Reduction Activities in Metabolic Syndrome

AIDS:	N	TOTALS	A	B	D
		Inpatient	0	0	0
START DATE:	3/1/2006	Scatter Bed	0	0	0
Total # pts expected for entire study:	5,643	Outpatient	0	0	0
		Scatter RN Hours	0	0	0
		Offsite Visits	0	0	0

RESEARCH BIONUTRITION	N	MULTICENTER STUDY	N
INFORMATICS CORE	N	CLINICAL TRIAL	N
BIostatistician	Y	CORE LAB	N
ANCILLARIES ONLY	N		

INVESTIGATOR	DEPARTMENT	NON-HOST INSTITUTION: STATE, COUNTRY
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WALSH, STEPHEN J SCD	Ctr for Biostatistics	
KENNY, ANNE M MD	CENTER ON AGING	

SUBPROJECT DESCRIPTION:

Metabolic syndrome is a major risk factor for cardiovascular disease (CVD). It involves the clustering of three or more of the following conditions -obesity, hypercholesterolemia, hyperglyceridemia, hypertension, and hyperglycemia. Available prevalence estimates suggest that 20-to-25 percent of the U.S. adult population currently have this syndrome. Numerous studies demonstrate that weight loss via changes in diet and exercise can reduce the severity, and even the existence, of these conditions. However, at the present time, no published investigation has reported on the frequency, circumstances, or success of weight reduction activities among persons with metabolic syndrome. The broad objective of the research outlined in this proposal is to address this gap in our understanding of metabolic syndrome and, thereby, to provide a basis for the formulation of public health initiatives that might reduce its severity, prevalence, and evolution into CVD. Using data from the National Health and Nutrition Examination Survey (NHANES) we will conduct statistical analyses to address the following questions:

1. Do individuals with metabolic syndrome perceive obesity and being overweight as a problem that needs to be addressed?
2. What nutritional and lifestyle changes are persons with metabolic syndrome undertaking in order to manage the condition and its effect on levels of CVD risk?
3. What factors enhance and/or inhibit the initiation of weight loss activities among persons with metabolic syndrome?
4. Which types of weight loss activities hold the most potential for achieving weight loss in those with metabolic syndrome? The project will utilize staff and expertise of the Biostatistics Core of the University of Connecticut General Clinical Research Center (GCRC) and faculty clinicians. The proposed project will contribute to our understanding of the scope and, perhaps, growth of the epidemic of metabolic syndrome in the U.S. population. It will also shed light on the simplest and most economical factors through which that epidemic might be controlled.

SUBPROJECT PROGRESS:

This project utilizes the GCRC Biostatistics Core to analyze data from the 1999-2000, 2001-2002, and 2003-2004 waves of the National Health and Nutrition Examination Survey (NHANES). Since the survey has already been administered by the National Center for Health Statistics, the project does not involve enrollment of new subjects at the University of Connecticut Health Center (UCHC) or within the GCRC. Because the project involves only the analysis of existing, publicly available data, the UCHC Institutional Review Board has determined that it does not constitute human subjects research. Therefore, there are no issues related to subject recruitment and no issues related patient safety. By the end of Year 13 of GCRC funding, statistical analyses for this project were substantially complete.

Study findings include the following: 1. demonstration that increases in the national prevalence of metabolic syndrome among adults in the United States continue to occur, having reached a level of approximately 34% during the 1999-2004 period; 2. discovery that metabolic syndrome develops through two distinct patterns of risk factors that appear to be determined substantially by age -one pattern that occurs primarily before age 40 and another that occurs primarily after age 50; 3. determination that, on an annual basis, approximately 50% of persons with metabolic syndrome who are overweight engage in some type of "weight loss" activity and that approximately 50% do not; 4. determination that, on an annual basis, less than 20% of persons with metabolic syndrome who are overweight succeed in intentionally losing 10 pounds or more; 5. demonstration that physician advice regarding overweight status, the

presence of other metabolic syndrome components (high blood pressure, high cholesterol, and diabetes), and the need for weight loss constitutes one of the strongest predictors both of the attempt to lose weight and of successful weight loss; 6. recognition that more than 40% of individuals with metabolic syndrome who are overweight report that they have never been told by their doctors that they are overweight.

Use of GCRC resources will continue into Year 14 of GCRC funding. The original deadline for project completion was April 14, 2007. Currently, we estimate that a manuscript summarizing study findings will be finished by August 31, 2007.

SPID: 0618 **PROTOCOL:** 618 **TYPE:** RESEARCH

SHORT TITLE: Girls in Recovery
LONG TITLE: Girls in Recovery from Life Stress (GIRLS)

AIDS:	N	TOTALS	_____		
			A	B	D
		Inpatient	0	0	0
START DATE:	2/16/2006	Scatter Bed	0	0	0
Total # pts expected for entire study:	52	Outpatient	0	0	0
		Scatter RN Hours	0	0	0
		Offsite Visits	0	0	0

RESEARCH BIONUTRITION	N	MULTICENTER STUDY	N
INFORMATICS CORE	Y	CLINICAL TRIAL	N
BIostatistician	N	CORE LAB	N
ANCILLARIES ONLY	N		

INVESTIGATOR	DEPARTMENT	NON-HOST INSTITUTION: STATE, COUNTRY
FORD, JULIAN D PHD	PSYCHIATRY	
ABU-HASABALLAH, KHAMIS PHD	Psychiatry	
ASTUR, ROBERT S PHD	OLIN CENTER	HARTFORD HOSPITAL, CT USA
MOFFITT, KATHIE H PHD	Psychiatry	
STEINBERG, KAREN L PHD	PSYCHIATRY	
STEVENS, MICHAEL C PHD	OLIN CENTER	HARTFORD HOSPITAL, CT USA
TENNEN, HOWARD PHD	Community Medicine	

SUBPROJECT DESCRIPTION:

The purpose of the GIRLS study is to provide counseling to adolescent girls in the juvenile justice system who are experiencing Post Traumatic Stress Disorder (PTSD) to help them regulate their emotions, planning, decision-making, and actions/ interactions in ways that will reduce PTSD and enhance their safety, responsible civic involvement, learning, peer, family, and adult relationships, and physical and psychological well-being.

The study will be the first randomized clinical trial of two promising manualized therapeutic interventions for complex post-traumatic stress disorder (PTSD): 1) Trauma Adaptive Recovery Group Education and Therapy (TARGET; Frisman, Ford, & Lin, 2004) and Life Skills/Life Story (LS/LS; Cloitre et al., 2002). Both interventions will provide 16 one-to-one educational and therapeutic sessions that teach coping skills and stress reduction techniques.

The aims of the study are:

- 1) To test how participation in TARGET and LS/LS relates to clinically and statistically significant improvements will occur in PTSD symptoms, psychosocial functioning, and emotion/impulse regulation;
- 2) To compare the differential affects of TARGET and LS/LS on affect regulation, social support, stress-related information processing and cognitive coping, and the reduction of impulsive or aggressive thinking/behavior;
- 3) To identify changes in daily self-regulation after TARGET and LS/LS; and 4) To identify alterations in brain activity that change after TARGET and LS/LS. An ethnically diverse sample (N=52) of juvenile justice-involved girls between 13 and 17 years of age will be recruited in clinic, community, detention, and residential programs. After screening for eligibility and obtaining valid signed consent forms, participants will be randomly assigned to one of the two experimental conditions. Within each condition, trained clinicians will administer 16 sessions of individualized counseling using manual for the specified intervention. Psychometric self-report and daily monitoring measures will be obtained at baseline, post-treatment, and 4-month follow-up assessments and multivariate statistical techniques will be used for analysis of treatment effects.

The research conducted highlights the need to address trauma among justice-involved youths. Most have experiences past traumas and many exhibit risk behaviors (substance use and suicidal ideation) that jeopardize their wellbeing and reduce their ability to engage in prosocial lifestyles. Contact with court-related services presents a critical window of opportunity. Juvenile justice agencies have the chance to identify at-risk youths through early screening and assessment and referral to age-appropriate and gender-sensitive treatment services.

SUBPROJECT PROGRESS:

Number of subjects enrolling during the report period and since initiation of the study: During report period: 50 Since initiation of the study: 52 Any changes in recruitment plans that might be needed: We may submit a request for modification in order to advertise the project via UCHC Broadcast Messages over the summer months. This is because we anticipate reduced recruitment from public school systems during the summer months Unexpected safety concerns and their resolution: There have been two unexpected, unrelated serious adverse events (SAEs). Both cases involved temporary hospitalizations due to psychiatric symptoms. These events were reported to the University of Connecticut Health Center (UCHC) and Connecticut Department of Children and Families (DCF) IRBs and the Court Supported Services Division (CSSD) IRRC as serious adverse events that were unexpected (not described in the informed consent forms) and unrelated to the study. One of the participants continued in the study after release from the hospital. We lost contact with the other participant subsequent to her hospitalization. The DCF IRB asked that changes be made to safety and safety reporting procedures these "to ensure that sufficient background and contextual information about potential participants is known at the earliest stages of the recruitment process, and that appropriate safety-related actions are taken for all girls regardless of their recruitment status." To that end, we have made several UCHC-approved protocol and consent form modifications, and are making additional protocol and related document revisions at the time of this report. All such revisions must first be reviewed and approved by the UCHC IRB, and then by the DCF IRB. Modifications are also sent to the UCHC GCRC at the time they are submitted to the UCHC IRB.

Interim data and outcomes if appropriate: N/A Any proposed changes made or anticipated in the protocol: As noted above under "recruitment changes", we may submit a request for modification in order to advertise the project via UCHC Broadcast Messages over the summer months. This is because we anticipate reduced recruitment from public school systems during the summer months Publications, indicating whether the GCRC was cited: No publications at this time.

SPID: 0620	PROTOCOL: 620	TYPE: RESEARCH
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SHORT TITLE: Pharmacokinetic Study

LONG TITLE: Pharmacokinetic Study of Single Dose Dutasteride in Healthy Subjects

AIDS:	N	TOTALS	A	B	D
		Inpatient	0	0	0
START DATE:	3/23/2006	Scatter Bed	0	0	0
Total # pts expected for entire study:	40	Outpatient	193	0	0
		Scatter RN Hours	0	0	0
		Offsite Visits	0	0	0

RESEARCH BIONUTRITION	N	MULTICENTER STUDY	N
INFORMATICS CORE	N	CLINICAL TRIAL	N
BIostatistician	Y	CORE LAB	Y
ANCILLARIES ONLY	N		

INVESTIGATOR	DEPARTMENT	NON-HOST INSTITUTION: STATE, COUNTRY
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COVAULT, JONATHAN MD, PHD	Psychiatry	
ARIAS, ALBERT MD	Psychiatry	
KRANZLER, HENRY R MD	PSYCHIATRY	

SUBPROJECT DESCRIPTION:

To monitor the inhibition of 5 α -reductase (5AR) enzyme activity at 1, 3, 7, 14, 21 and 28 days following administration of a single dose of dutasteride (2, 3, or 4 mg) by measuring the change in blood levels of 3 α -androstanediol glucuronide (3 α -diolG) and the ratio of dihydrotestosterone (DHT) to testosterone. To accomplish this aim, an open-label, between-subjects dose comparison study design will be employed with subjects receiving a 2, 3, or 4 mg dosage. Subjects (up to n=40 enrolled to allow a minimum of 24 completers) will be randomly assigned to one of the 3 dose levels. Results of this study will inform the dose selection for a subsequent placebo-controlled, within-subject, crossover study of dutasteride on the effects of alcohol. A secondary aim of this study is to examine the correlation of a genetic variation in the type I 5AR gene and baseline DHT/T ratio and effect of dutasteride at day 3. A variation in this gene, whose product is one of the targets of dutasteride, has been reported to be associated with higher baseline levels of DHT.

SUBPROJECT PROGRESS:

Subject enrollment for this study was completed on 11/21/06. A total of 26 subjects were enrolled into the study during the report period. The last subject completed participation of this study on 01/02/07. There were no unexpected safety concerns associated with this study. No subjects experienced serious adverse events. No subjects dropped out of the study due to adverse experiences related to the study medication. There were several changes to the protocol during the report period. In order to increase the potential pool of volunteers, the age range for subject participation was changed from 21-45 years old to 21-55 yrs old. Screening visit compensation was increased from \$25.00 to \$50.00 in order to more fairly compensate subjects for their travel time and expense, inconvenience of a blood draw, a 1 hour screening evaluation and ingestion of 4-8 capsules of study medication all of which occurred at the screening visit. We obtained Institutional Review Board (IRB) approval to conduct follow-up visits at the Psychology Department on the University of Connecticut Health (UConn) Storrs campus for individuals from UConn Storrs to reduce travel barriers to participation. Recruitment plans for the study did not change during the report period. Enrollment has ended and hormone laboratory assays have been completed. With regard to the primary aim, as expected dutasteride reduced the concentration of 5-alpha reductase hormone metabolites, this was evident in examination of either dihydrotestosterone or 3 α -androstanediol glucuronide. The later metabolite showed less variation between subjects and a more consistent pattern of change overtime. These results validate the future use of 3 α -androstanediol glucuronide as a marker of dutasteride in our GCRC protocol #619 study. Our results indicate that the 4 mg dose provides more consistent inhibition (80%) of enzyme activity in the 3-7 day window during which we plan to study the effect of dutasteride pre-treatment on alcohol responses in GCRC protocol 619. The inhibition was progressively reduced in the 2-4 week interval and was reversed at all doses by 6 weeks. There were significant individual differences in the degree of hormone metabolite change which will be the focus of a secondary pharmacogenetic analysis of these data once genotype information for the two isoforms of 5-alpha reductase is obtained. Study medication was well tolerated at the 2mg, 3mg, and 4mg dose. GCRC support will be cited in any manuscript based on this study. We request continued GCRC Core Lab support for this project for additional genotyping of the Deoxyribonucleic acid (DNA) samples collected in this study.

SPID: 0621	PROTOCOL: 621	TYPE: RESEARCH
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SHORT TITLE: PACTG 1058

LONG TITLE: Pediatric Aids Clinical Trials Group (PACTG) 1058: Intensive Pharmacokinetic Studies of Antiretroviral Drug Combinations in HIV Positive Children

AIDS:	Y	TOTALS	A	B	D
			Inpatient	0	0
START DATE:	3/20/2006	Scatter Bed	0	0	0
Total # pts expected for entire study:	2	Outpatient	1	0	0
		Scatter RN Hours	0	0	0
		Offsite Visits	0	0	0

RESEARCH BIONUTRITION	N	MULTICENTER STUDY	Y	
INFORMATICS CORE	Y	CLINICAL TRIAL	Y	Phase III
BIostatistician	N	CORE LAB	N	
ANCILLARIES ONLY	N			

INVESTIGATOR	DEPARTMENT	NON-HOST INSTITUTION: STATE, COUNTRY
SALAZAR, JUAN C MD	PEDIATRICS	
FEDER, HENRY MD	Medicine/Family Medicine	
KRAUSE, PETER MD	Pediatrics	

SUBPROJECT DESCRIPTION:

The study, entitled Intensive Pharmacokinetic Studies of Antiretroviral Drug Combinations in Children is an intensive 12-hour pharmacokinetic study of selected antiretroviral drugs in Human Immunodeficiency Virus (HIV)-infected children who are receiving or about to initiate a regimen of antiretrovirals that includes one of three drug combinations of non-nucleoside reverse transcriptase inhibitors (NNRTI) and protease inhibitors (PI). These combinations include drugs that may not be labeled for marketing for use in children (for example saquinavir {Invirase}). The optimal dosages or combination of dosages may not be known for the pediatric population. Labeling information cannot be determined until more pharmacokinetic information has been collected and analyzed. Despite this limited information, the current Centers for Disease Control (CDC) Pediatric HIV Treatment Guidelines allows use of these medications; and more importantly, there are times when a child's individual viral load and resistance profile (genotype and phenotype) clinically indicates the use of these combinations. Therefore it is vital to obtain better information about the pharmacokinetics of these combinations currently in use by today's pediatric infectious disease specialists. This information will ultimately lead to more appropriate and effective dosing for the pediatric and adolescent population, as well as the subjects who participate in this protocol.

SUBPROJECT PROGRESS:

PACTG 1058 (Version 1.0) has had one HIV-infected enrollment in the past report period. There have been two enrollments since initiation of the study.

Due to funding changes throughout the PACTG/IMPAACT Network, we will no longer be able to offer this protocol.

SPID: 0622 **PROTOCOL:** 622 **TYPE:** RESEARCH

SHORT TITLE: Partner violence

LONG TITLE: The temporal relationships of partner violence and drug use

AIDS:	N	TOTALS	A	B	D
		Inpatient	0	0	0
START DATE:	3/22/2006	Scatter Bed	0	0	0
Total # pts expected for entire study:	60	Outpatient	0	0	0
		Scatter RN Hours	0	0	0
		Offsite Visits	0	0	0

RESEARCH BIONUTRITION	N	MULTICENTER STUDY	N
INFORMATICS CORE	Y	CLINICAL TRIAL	N
BIostatistician	N	CORE LAB	N
ANCILLARIES ONLY	N		

INVESTIGATOR	DEPARTMENT	NON-HOST INSTITUTION: STATE, COUNTRY
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SULLIVAN, TAMI P PHD	FAMILY VIOLENCE RESEARCH A	YALE UNIVERSITY, CT USA
ABU-HASABALLAH, KHAMIS PHD	Psychiatry	

SUBPROJECT DESCRIPTION:

As evidenced by a number of current initiatives such as National Institute of Drug Abuse (NIDA's) initiative on stress and drug abuse, Healthy People 2010, and the National Institute of Health (NIH) Agenda for Research on Women's Health for the 21st Century, the relationship between substance abuse and violence has become a national priority. Moreover, although research demonstrates associations between intimate partner violence (IPV) victimization and the development of substance use disorders among women, this phenomenon has not been adequately examined (NIDA, 2003b; Wekerle & Wall, 2002). This is of particular concern because women, by virtue of substantially higher risks of victimization (Dansky, Byrne, & Brady, 1999), may be at increased risk to use substances to cope with their tension and stress. A gap exists in the literature in its ability to explain this complex temporal relationship within a single episode and, across multiple episodes over time. This gap was the catalyst for the current study which will gather information regarding the temporal relationships of IPV events to substance use among a community sample of 180 abused women. Specific aims are; a) to gather pilot data on the temporal relationship of substance use and IPV events, and b) to examine the effectiveness of three methods of data collection 1) paper diaries; 2) monthly, retrospective, semi-structured interviews; and 3) telephone data collection methods. For each data collection condition, feasibility will be assessed by a) compliance with the instructions, b) perceived safety in completing assessments, c) reported honesty, d) reported ease, e) preference for methodology assigned, or alternate methodology, f) percent attrition by methodology, and g) degree and pattern of missing data. *** The only participants to have contact with the GCRC would be those participating in the telephone data collection condition (i.e., approximately 60 participants).

SUBPROJECT PROGRESS:

The study is still under development. The work that was done during this reporting period was on the development of the protocol and the programming of questionnaire into the Interactive Voice Response (IVR) system. No participants have been enrolled in the study. Pilot testing is expected to commence this summer. No publications have been written about this study.

SPID: 0623 **PROTOCOL:** 623 **TYPE:** RESEARCH

SHORT TITLE: Contingency Management

LONG TITLE: Contingency Management for Substance Abuse Treatment

AIDS:	N	TOTALS	A	B	D
		Inpatient	0	0	0
START DATE:	4/30/2006	Scatter Bed	0	0	0
Total # pts expected for entire study:	269	Outpatient	0	0	0
		Scatter RN Hours	0	0	0
		Offsite Visits	1,614	0	0

RESEARCH BIONUTRITION	N	MULTICENTER STUDY	N
INFORMATICS CORE	N	CLINICAL TRIAL	N
BIostatistician	N	CORE LAB	N
ANCILLARIES ONLY	N		

INVESTIGATOR	DEPARTMENT	NON-HOST INSTITUTION: STATE, COUNTRY
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PETRY, NANCY M PHD	PSYCHIATRY	
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ALESSI, SHELIA PHD	Psychiatry	
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SUBPROJECT DESCRIPTION:

Contingency management (CM) interventions are highly efficacious in improving substance abuse treatment outcomes. These interventions have been provided primarily in an individual format, but most therapy for substance abusers is delivered in the context of groups. We have preliminary data suggesting that our prize-based CM, which is substantially less costly than traditional voucher-based CM, can be administered in a group setting. This study will evaluate the efficacy of prize-based CM when administered exclusively in groups. Substance dependent patients beginning intensive outpatient day treatment (N=360) at one of three community-based programs will be randomly assigned to one of two conditions: (a) standard, non-CM treatment or (b) standard treatment plus prize CM delivered in groups. In the CM condition, patients will earn the opportunity to win prizes ranging from \$1 to \$100 in value for attending groups and submitting drug-free biological specimens. Substance use and psychosocial problems will be measured at intake, month 1, month 3 (post treatment), and at 6-, 9-, and 12-month follow-up evaluations.

We will also assess patient characteristics that may be associated with improved outcomes within and across conditions. We will evaluate the cost-effectiveness of group-based CM by assessing receipt of psychosocial and medical services and criminal justice system involvement throughout the treatment and follow-up periods.

SUBPROJECT PROGRESS:

Total Enrollment: 192 Past Year Enrollment: 84 · No changes in recruitment plans are needed. · No unexpected safety concerns have occurred. · Interim data and outcomes are not available. · Changes to protocol: 1) Changed the list of recruitment sites in the study protocol to include only the three active sites where study procedures are taking place. 2) Changed the amount in the protocol that incarcerated subjects receive for the Month 1 follow-up to \$20. · No publications to date.

SPID: 0624	PROTOCOL: 624	TYPE: RESEARCH
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SHORT TITLE:	Omega-3
LONG TITLE:	Effects of Omega-3 Fatty Acids on Bone and Fragility

AIDS:	N	TOTALS	A	B	D
			Inpatient	0	0
START DATE:	4/20/2006	Scatter Bed	0	0	0
Total # pts expected for entire study:	150	Outpatient	139	0	0
		Scatter RN Hours	0	0	0
		Offsite Visits	0	0	0

RESEARCH BIONUTRITION	N	MULTICENTER STUDY	N
INFORMATICS CORE	N	CLINICAL TRIAL	N
BIostatistician	Y	CORE LAB	Y
ANCILLARIES ONLY	N		

INVESTIGATOR	DEPARTMENT	NON-HOST INSTITUTION: STATE, COUNTRY
KENNY, ANNE M MD	CENTER ON AGING	
LAMMI, KEEFE PHD	NUTRITIONAL SCIENCE	UCONN, STORRS, CT USA
PILBEAM, CAROL C MD, PHD	MEDICINE	
SECOR, ERIC R MD	IMMUNOLOGY	
THRALL, ROGER S PHD	MEDICINE/PULMONARY	
WALSH, STEPHEN J SCD	Ctr for Biostatistics	

SUBPROJECT DESCRIPTION:

Osteoporosis is a bone thinning disease that results in fractures that occur with minimal trauma. The direct health care costs related to osteoporosis are estimated to be 14 billion dollars per year, comparable to costs in heart failure and asthma. Frailty or poor physiologic reserve to deal with stressors, in the general population over age 65 is estimated to be 7%; frailty is associated with an increase risk of falls and fracture. Both osteoporosis and frailty are thought to have inflammation as a contributing factor. Omega-3 fatty acids found in fish oil [eicosapentaenoic acid (EPA, 20:5n-3) and docosahexaenoic acid (DHA, 22:6n-3)] have been shown to decrease markers of inflammation (cytokines) and decrease death due to heart disease. A number of studies in animals suggest that fish oil (or EPA and DHA supplementation) inhibits bone break down, increases calcium absorbed from the diet and enhances calcium in bone. Studies done in humans are few. The studies have used a mix of essential fatty acids including n-6 and n-3 fatty acids. N-6 fatty acids are thought to increase inflammation while n-3 fatty acids are thought to decrease inflammation. The effects of the fatty acids appear to depend on the level of n-6 to n-3. In one study, investigators demonstrated that n-6/n-3 fatty acid mixture supplementation increased bone mineral density or bone thickness of the spine and hip over 18 months in a group of older, nursing home residents with osteoporosis or low bone mass. As far as we know, no study has evaluated the role of n-3 fatty acids in the frailty syndrome, characterized by sarcopenia or muscle loss, inflammation, low estrogen, growth hormone and testosterone levels, poor nutrition and disability.

SUBPROJECT PROGRESS:

This study is actively underway. We have received 220 calls with interest. We found 87 not eligible at telephone screening. One hundred and thirty three were scheduled for a screening visit. Of these individuals, 66 were noneligible after the visit and 67 were found to be eligible. Forty-eight baseline visits have been completed. Two individuals have dropped out of the study, one due to study burden and another due to "aches and pains" caused by the study medication. The recruitment goals are 150 women. We will continue to recruit for the study in the upcoming year.

SPID: 0625 **PROTOCOL:** 625 **TYPE:** RESEARCH

SHORT TITLE: Androgen Receptor

LONG TITLE: Androgen Receptor Polymorphisms in East Asian Men

AIDS:	N	TOTALS	A	B	D
		Inpatient	0	0	0
START DATE:	5/18/2006	Scatter Bed	0	0	0
Total # pts expected for entire study:	50	Outpatient	0	0	0
		Scatter RN Hours	0	0	0
		Offsite Visits	0	0	0

RESEARCH BIONUTRITION	N	MULTICENTER STUDY	N
INFORMATICS CORE	N	CLINICAL TRIAL	N
BIostatistician	N	CORE LAB	Y
ANCILLARIES ONLY	N		

INVESTIGATOR	DEPARTMENT	NON-HOST INSTITUTION: STATE, COUNTRY
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RAJAN, THIRUCHANDURAI V MD,
PHD

Pathology

SUBPROJECT DESCRIPTION:

The specific aim is to examine androgen receptor polymorphisms that have been associated with increased risk of osteoporosis and bone fracture. The hypothesis driving this proposal is that the androgen receptor genes of ethnic East Asian Indians will encode a protein with larger numbers of glutamine residues than other groups.

SUBPROJECT PROGRESS:

We recruited 49 males of East Asian Indian ancestry for the study. Each was given a cup to spit into. Deoxyribonucleic acid (DNA) was extracted according to manufacturer's directions. The CAG polymorphism in the first exon of the androgen receptor gene was amplified using the following primers: CACCTCCGCGCCA (fwd) and AGAACCATCCTCACCTGCTG (rev). The products were analyzed on a denaturing sequencing gel. We are in the process of analyzing the data. Preliminary analyses reveal that there is a statistically significant difference between the mean CAG polymorphism length in East Asian Indian men compared to historic data on males of European ancestry. We are planning to write a brief report on our findings.

SPID:	0626	PROTOCOL:	626	TYPE:	RESEARCH	
SHORT TITLE:	Asthma					
LONG TITLE:	Genes, Home Allergens and Asthma in Puerto Rican Children					
AIDS:	N	TOTALS		A	B	D
		Inpatient		0	0	0
START DATE:	5/18/2006	Scatter Bed		0	0	0
Total # pts expected for entire study:	100	Outpatient		49	0	0
		Scatter RN Hours		0	0	0
		Offsite Visits		69	0	0
RESEARCH BIONUTRITION	N	MULTICENTER STUDY		N		
INFORMATICS CORE	Y	CLINICAL TRIAL		N		
BIostatistician	N	CORE LAB		N		
ANCILLARIES ONLY	N					

INVESTIGATOR	DEPARTMENT	NON-HOST INSTITUTION: STATE, COUNTRY
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CLOUTIER, MICHELLE M MD	PEDIATRICS	
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SUBPROJECT DESCRIPTION:

Asthma affects over 14 million people in the United States.¹ The prevalence of asthma in the U.S. increased by 74.9% from 1980 to 1996; 1 ethnic minority populations such as Puerto Ricans are disproportionately represented in this trend of increasing asthma morbidity. 2, 3 Puerto Ricans had the highest age-adjusted asthma mortality from 1990 to 1995 among U.S. Hispanics in general and among Hispanics in the U.S. Northeast in particular. Although asthma is a major public health problem among Puerto Ricans, little is known about the contribution of genetic and environmental factors to asthma in this population. 5 To date, results of genome-wide analyses for linkage to asthma phenotypes have been published by 11 groups in 13 distinct populations. 6-17 None of these genome scans included Puerto Ricans. Because of the high prevalence of single-parent households among Puerto Ricans in the U.S. mainland,¹⁸ family-based studies of genetic association would be difficult to perform in this population. A population-based case-control study of genetic association for asthma and asthma-related phenotypes among Puerto Ricans in the U.S mainland is feasible and would offer a unique opportunity to examine genetic and environmental risk factors in a minority population with high asthma morbidity. We have recruited children with asthma in Hartford (Connecticut) as part of a program to improve asthma management by physicians in this community.¹⁹ In these children, we have shown that Puerto Rican ethnicity is associated with sensitization to specific allergens and increased asthma severity.^{20, 21} Among school children in Hartford, we have collected data in a group of Puerto Rican children with asthma (cases) and a group of Puerto Rican children without asthma (controls). We propose to conduct a case-control study of association between selected genetic and environmental factors and asthma in Puerto Ricans. Between 75% and 94% of Puerto Rican children with asthma are atopic (see C.4.c).²² In atopic children, production of cytokines (IL-4, IL-5, IL-9, and IL-13) by T-helper (Th)2 cells promotes increased production of immunoglobulin E (IgE), eosinophilia, mast cell differentiation, and long-term expression of allergen-specific immunity.^{23,24} Atopy and atopic asthma may result from lack of upregulation of Th1 immune responses and/or inadequate downregulation of Th2 immune responses.^{25, 26} We hypothesize that single nucleotide polymorphisms (SNPs) in genes that control the development and regulation of Th1 cells, Th2 cells, and regulatory T cells (Tregs) are associated with asthma and/or intermediate phenotypes of asthma (asthma phenotypes") in Puerto Rican children. We further hypothesize that parental report of exposure to pets in early life (during pregnancy and/or the first year of life) is associated with reduced risks of asthma and atopy, and that current exposure to high levels of indoor allergens is associated with a) increased asthma severity and abnormal lung function phenotypes (reduced FEV1 and FEV1/FVC, increased airway responsiveness, and reduced bronchodilator responsiveness) in Puerto Rican children with asthma and b) atopy phenotypes (e.g., increased serum total IgE) in Puerto Rican children with and without asthma. In addition, we hypothesize that variants in genes that control the development and regulation of Th1 cells, Th2 cells, and Tregs interact with indoor allergen exposures in influencing asthma and asthma severity in Puerto Rican children.

To test these hypotheses, we will pursue the following specific aims: 1. To recruit 500 Puerto Rican children with asthma (cases) and 500 Puerto Rican children without asthma (control subjects). 2. To test for association between Single Nucleotide Polymorphisms (SNPs) in 20 positional candidate genes and i) asthma (in all subjects), ii) lung function phenotypes (airway responsiveness, FEV1, FEV1/FVC, and bronchodilator response) and atopy phenotypes (skin test reactivity to allergens, serum total and allergen-specific IgE, and eosinophil count) separately in cases and in control subjects, and iii) asthma severity in cases. 3a. To examine whether i) parental report of exposure to pets (dogs and/or cats) in early life is associated with reduced risks of asthma (in all subjects) and atopy (separately in cases and in control subjects), and b) current exposure to indoor allergens (dust

mite, cockroach, dog, cat, mouse, and rat) is associated with increased asthma severity and abnormal lung function phenotypes in cases, and with atopy phenotypes separately in cases and in control subjects. 3b. To examine interactions between exposure to the indoor allergens outlined in Specific Aim 3a and SNPs in the candidate genes selected in Specific Aim 2.

SUBPROJECT PROGRESS:

During the time period from 4/01/06 - 3/31/07 we have enrolled a total of 65 children into our genetic study. From 1/26/01 - 5/18/07, we have enrolled a total of 189 children; of this total, 8 children have dropped from the study (we discovered that both parents and grandparents of 3 children were not Puerto Rican, 1 child had a mild case of cerebral palsy and was unable to perform pulmonary function, and 4 children/families were no longer interested in participating). Our primary recruitment strategy consists of distributing a recruitment flyer to 14 area schools, attending parent/teacher conferences, and providing presentations on the topic of asthma at PTO (Parent Teacher Organization) meetings. To date, we have targeted 7 area schools and we plan to continue our recruitment through the summer months at the various Boys and Girls Club locations in Hartford. We will resume school recruitment in Fall 2007 when classes are in session. To date, we have not experienced any unexpected safety issues and we do not anticipate any safety concerns. We have not performed any data analysis; however, we plan to review the interim data when we have completed a total of 200 home visits. Small protocol changes have occurred and each has been reviewed and approved by the Connecticut Children's Medical Center (CCMC) Institutional Review Board (IRB), the IRB of record: we have begun collecting (1) 4 ml red top for serum collection. We continue to collect (2) 10 ml purple tops for DNA testing and (1) 4ml purple top for CBC (Complete Blood Count), and (1) 6 ml red top for RAST and IgE testing. The amount of blood we draw remains small, and thus, we do not anticipate any additional risk to our participants. To date, the blood drawing has been very well tolerated by the children. We do not foresee additional changes to the protocol. To date, we have not published any work related to the "Genes, Home Allergens and Asthma in Puerto Rican Children" study.

SPID: 0627	PROTOCOL: 627	TYPE: RESEARCH
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SHORT TITLE: Social Marketing

LONG TITLE: Place-based Social Marketing to Prevent Urban Youth Party Drug Use

AIDS:		TOTALS	A	B	D
	N	Inpatient	0	0	0
START DATE:	5/18/2006	Scatter Bed	0	0	0
Total # pts expected for entire study:	600	Outpatient	0	0	0
		Scatter RN Hours	0	0	0
		Offsite Visits	0	0	0

RESEARCH BIONUTRITION	N	MULTICENTER STUDY	N
INFORMATICS CORE	Y	CLINICAL TRIAL	N
BIostatistician	N	CORE LAB	N
ANCILLARIES ONLY	N		

INVESTIGATOR	DEPARTMENT	NON-HOST INSTITUTION: STATE, COUNTRY
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SCHENSUL, JEAN PHD	INST FOR COMM RESEARCH	UConn - Storrs, CT USA
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SUBPROJECT DESCRIPTION:

The purpose of this three year project, entitled "Place-based Social Marketing to Prevent Party Drug Use among Urban Youth" is to demonstrate the efficacy of entertainment shows containing drug prevention messages in supporting urban youth aged 16-20 to maintain drug free lifestyles in communities where alcohol, marijuana and ecstasy are the most widely used social or "party" drugs.

The aims of the proposed intervention pilot study are thus the following:

AIM 1: To conduct a drug prevention intervention based on critical components of youth culture that integrates cognitive behavioral, social marketing, and entertainment-education theories in Hartford and New Haven with two cohorts of non-using urban youth 16 - 20.

A. To brand (to create a brand name/image, e.g., Xperience-Hartford, Xperience-New Haven) an approach to drug-free "shows," and develop a set of related culturally congruent messages based on urban youth core values (e.g. respect, loyalty, power), party drug expectancies and known patterns of social influence to reinforce resistance to party drug use in urban African American and Puerto Rican/Latino non-users or experimenters.

B. To integrate these messages into culturally relevant channels, utilizing the "show" as the primary venue, and test messages-plus-channels for feasibility and acceptability in focus groups

AIM 2. To evaluate the short-term efficacy of the prevention intervention against matched community control groups using a quasi-experimental crossover design with pre- and immediate post-test observation points and Interactive Voice Response (IVR), an automated telephone data entry technology.

AIM 3. To produce a procedural manual and audiovisual product for dissemination of the intervention model to other sites and promoters in urban areas throughout the country.

Hypothesis #1: Youth exposed to the Xperience prevention intervention will report lower party substance use and higher drug abstinence peer norms than a comparable group of unexposed youth from a matched community (control group).

Hypothesis #2: Level of absorption, attitudes, and expectancies will mediate desired outcomes (peer norms and substance use behaviors) in the intervention group.

SUBPROJECT PROGRESS:

This study was approved by the GCRC Scientific Advisory Committee in May of 2006. Due to no activity, the Principal Investigator (PI) terminated the study in the GCRC on 8/23/2006.

SPID: 0628	PROTOCOL: 628	TYPE: RESEARCH
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SHORT TITLE: Discrimination Stress

LONG TITLE: Daily process pilot study of discrimination stress and diabetes outcomes in African American Women

AIDS:	N	TOTALS	A	B	D
		Inpatient	0	0	0
START DATE:	5/30/2006	Scatter Bed	0	0	0
Total # pts expected for entire study:	10	Outpatient	5	0	0
		Scatter RN Hours	0	0	0
		Offsite Visits	0	0	0

RESEARCH BIONUTRITION	N	MULTICENTER STUDY	N
INFORMATICS CORE	Y	CLINICAL TRIAL	N
BIostatistician	N	CORE LAB	Y
ANCILLARIES ONLY	N		

INVESTIGATOR	DEPARTMENT	NON-HOST INSTITUTION: STATE, COUNTRY
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WAGNER, JULIE PHD	Behavioral Sci & Comm Hlth	
TENNEN, HOWARD PHD	Community Medicine	
WHITE, WILLIAM MD	Medicine/Hypertension	

SUBPROJECT DESCRIPTION:

Our group is investigating the influence of racial discrimination on diabetes outcomes among African American (AA) women. Our next step is an National Institute of Health (R01) for a daily process study that will test the hypotheses that glycemia, blood pressure, and health behaviors will be more affected by daily stress in women with high lifetime discrimination than their low discrimination counterparts. The pilot project proposed here will collect data to support that R01 application regarding the feasibility of the data collection, the acceptability of the protocol to participants, and the effect sizes among relationships. Ten diabetic AA women will wear continuous glucose sensor and ambulatory blood pressure monitoring equipment for 3 consecutive days, and report health behaviors for 7 consecutive days. Twice daily, participants will provide data on daily stressors using an interactive voice response telephone system. Information regarding recruitment, retainment, participant burden, effect sizes, technical challenges with data collection, and modification of questionnaires for daily assessment will increase the likelihood of a successful R01 application.

SUBPROJECT PROGRESS:

From 4/1/2006 until 3/31/2007, the Interactive Voice Response (IVR) survey was created and tested, the blood glucose monitoring system was purchased and staff was trained in its usage. Staff was also trained to use ambulatory blood pressure (bp) monitor and actigraph. During this period, 3 women enrolled and completed this pilot study. Several modifications to the project approved by Institutional Review Board (IRB) this year include: 1) Approval of a partial waiver of consent solely for the phone screen phase of the study 2) A change in funding source upon receiving award from Health Disparities Seed Grant, Latino Health Disparities NIH EXPORT Center, Department of Nutritional Sciences, UConn, Storrs 3) Correction made to Data Safety Monitoring Plan (DSMP) to add that the stored blood samples would be identified with an identification number that can be linked back to participant's data. 4) A change in inclusion criteria to include only post-menopausal women and peri-menopausal women, and to exclude premenopausal women. All other inclusion/exclusion criteria remain the same 5) A change from use of a pedometer to an actigraph to measure physical activity 6) A change to the protocol increasing number of days participants are asked to wear the Continuous Glucose Sensor (from 2 consecutive days to 5 consecutive days) and the ambulatory blood pressure monitor (from 3 consecutive days to 2 consecutive days). 7) Approval of a change in staff removing Dr. George Mansoor (who is no longer with UCHC) from the study team. Drs. William White and Madhavi Mallareddy were added as co-investigators 8) Addition of a packet of 19 standardized self-report assessments 9) Approval of two handouts to provide participants with easy to understand instructions for blood pressure monitors and continuous glucose sensors. 10) Changes were made to Informed Consent Form (ICF) and protocol to reflect the above changes. There are no unexpected safety concerns. There are no publications at this time.

SPID: 0629 **PROTOCOL:** 629 **TYPE:** RESEARCH

SHORT TITLE: ATOM

LONG TITLE: Contingency Management Reinforcement for Adolescent Cannabis Abuse

AIDS:	N	TOTALS	A	B	D
		Inpatient	0	0	0
START DATE:	6/15/2006	Scatter Bed	0	0	0
Total # pts expected for entire study:	72	Outpatient	108	0	0
		Scatter RN Hours	0	0	0
		Offsite Visits	0	0	0

RESEARCH BIONUTRITION	N	MULTICENTER STUDY	N
INFORMATICS CORE	N	CLINICAL TRIAL	N
BIostatistician	N	CORE LAB	N
ANCILLARIES ONLY	N		

INVESTIGATOR	DEPARTMENT	NON-HOST INSTITUTION: STATE, COUNTRY
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KAMINER, YIFRAH PHD	Psychiatry	
BURLESON, JOSEPH PHD	Behavioral Sciences	

SUBPROJECT DESCRIPTION:

The specific hypotheses to be tested are 1) Implementation of Voucher Based Reinforcement Therapy (VBRT) for youth with Cannabis Use Disorder is feasible and acceptable for both youths and therapists; 2) VBRT for youth produces a reduction of cannabis use during and at the completion of treatment; and 3) VBRT reinforcement for youth enhances a superior reduction of cannabis use relative to the non-reinforcement control condition. The proposed trial follows the guidelines for a preliminary Stage I study developed by the National Institute of Drug Abuse (NIDA) (Rounsaville et al., 2001). The goals of a Stage I project are 1) to determine whether or not a Stage II project is indicated for the therapy examined in a Stage I project, and 2) if so, provide the necessary procedures, manuals, measures, and data needed to support a Stage II application (e.g., effect size estimates). Decision on appropriateness of Stage II project implies that the data generated supports the feasibility and clinical utility of the therapy examined for that condition, and/or behavior that it is designed to treat.

SUBPROJECT PROGRESS:

Number of subjects enrolled during the report period and since initiation of the study: 35 No changes in recruitment plans are needed. No safety concerns. No interim data and outcomes are available at this juncture. No proposed changes made or anticipated in the protocol. No publications completed yet.

SPID: 0630	PROTOCOL: 630	TYPE: RESEARCH
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SHORT TITLE: Student Daily Life Experiences

LONG TITLE: Howard University Study of College Student Daily Life Experiences and the Interaction of Genetic Variation

AIDS:	N	TOTALS	A	B	D
		Inpatient	0	0	0
START DATE:	6/15/2006	Scatter Bed	0	0	0
Total # pts expected for entire study:	330	Outpatient	0	0	0
		Scatter RN Hours	0	0	0
		Offsite Visits	0	0	0

RESEARCH BIONUTRITION	N	MULTICENTER STUDY	Y
INFORMATICS CORE	Y	CLINICAL TRIAL	N
BIostatistician	N	CORE LAB	Y
ANCILLARIES ONLY	N		

INVESTIGATOR	DEPARTMENT	NON-HOST INSTITUTION: STATE, COUNTRY
COVAULT, JONATHAN MD, PHD	Psychiatry	
HERMAN, AREY BA	Psychiatry	
KRANZLER, HENRY R MD	PSYCHIATRY	
SCOTT, DENISE BS	GENETICS	HOWARD UNIVERSITY, DC USA
TAYLOR, ROBERT E MD	PHARMACOLOGY	HOWARD UNIVERSITY, DC USA
TENNEN, HOWARD PHD	Community Medicine	
WILLIAMS, CARLA PHD	MEDICINE	HOWARD UNIVERSITY, DC USA

SUBPROJECT DESCRIPTION:

This study is designed to evaluate the day-to-day associations among alcohol use, school-related behaviors, stressful events and mood states over the course of a one month period. Specifically, this study uses a web-based daily report tool to focus on how individuals cope with stressful daily events and negative mood states and, in turn, how coping efforts and mood affect alcohol use. Additionally, this project will examine (a) the influence of a functional polymorphism, 5-HTTLPR, in the promoter region of the serotonin transporter gene (as well as two other variations in this gene), and alcohol dependence associated haplotypes of the GABRA2 and GABRG1 genes encoding the α 1 subunits of the GABAA receptor on the use of alcohol by college students, and (b) evaluate the interactive effects of genotypes with daily life stressors, positive experiences, social interactions/peer influences, and positive or negative mood states on the use of alcohol by college students. In an exploratory aim we will also examine the effects of variation in other neurotransmitter related genes including: i) Monoamine oxidases (MAOA) which encodes monoamine oxidase, a key enzyme involved in metabolic inactivation of synaptic serotonin (as well as norepinephrine and dopamine), ii) Tph2 which encodes the brain specific form of tryptophan hydroxylase, the rate limiting enzyme in serotonin synthesis, iii) a functional promoter variant of the serotonin 5-HT1A presynaptic autoreceptor gene HTR1A and iv) CB-1 which encodes the brain form of the cannabinoid receptor and is thought to be involved in the regulation of appetitive and substance use behaviors.

This study will follow a protocol used in a parallel ongoing multi-year longitudinal study of college student daily life experiences at the University of Connecticut (UConn), Storrs, CT. By comparing results from these two campuses we hope to compare and contrast the influence of mood states, life events and genetic variation on alcohol use behaviors to identify shared and unique characteristics for the two college student samples. This cross sectional study at Howard University will provide important information about the feasibility of using methodologies developed at UCHC / Storrs sites at other college campuses to examine the generalizability of findings from our current Alcohol Research Center / GCRC study at the Storrs campus.

SUBPROJECT PROGRESS:

GCRC Annual report April 1, 2006 - March 31, 2007 Protocol: GCRC 630 - Howard University Study of College Student Daily Life Experiences and the Interaction of Genetic Variation. PI: Jonathan Covault 1) Number of subjects enrolled during the report period: 149 since initiation of study: 149 2) Planned changes in recruitment plans: none 3) Unexpected safety concerns and their resolution: None occurred. 4) Interim data: 49 subjects enrolled during initial pilot semester fall 2006 and 102 during the spring 2007 semester. Web based daily process phenotype data collected and in process of cleaning and conversion to useable database formats. Salivary Deoxyribonucleic acid (DNA) currently being prepared by the GCRC Core Lab for genotyping in next grant period. 5) Proposed

changes made or anticipated in the protocol: None 6) Publications for this study: none to date.

SPID:	0632	PROTOCOL:	632	TYPE:	RESEARCH	
SHORT TITLE:	Racism in Minority Children					
LONG TITLE:	Perceptions of Racism in Minority Children					
AIDS:	N	TOTALS		A	B	D
		Inpatient		0	0	0
START DATE:	6/20/2006	Scatter Bed		0	0	0
Total # pts expected for entire study:	600	Outpatient		0	0	0
		Scatter RN Hours		0	0	0
		Offsite Visits		47	0	0
RESEARCH BIONUTRITION	N	MULTICENTER STUDY		N		
INFORMATICS CORE	Y	CLINICAL TRIAL		N		
BIostatistician	N	CORE LAB		N		
ANCILLARIES ONLY	N					

INVESTIGATOR	DEPARTMENT	NON-HOST INSTITUTION: STATE, COUNTRY
PACHTER, LEE M MD	PEDIATRICS	CONNECTICUT CHILDREN'S MEDICAL CENTER, CT USA

SUBPROJECT DESCRIPTION:

The objective of this project is 1)to gain an understanding of the ways children of different ethnic minority backgrounds perceive, interpret, conceptualize, and process racism (racial discrimination and prejudice). 2)to utilize this information to create valid and reliable instruments for measuring perceptions of racism in minority children which will be based on developmental theory and which have saliency for children of different ethnicities, and 3)to use these instruments in studies aimed at understanding the effects of perceived racism on a]the developmental competencies and behavioral health of minority children, as well as b]disparities in health and health care outcomes seen in minority populations. Institutional Review Board (IRB) approval is being sought for Objective 2: the creation and testing of instruments (questionnaires) aimed at measuring perceptions of racism in minority children. A proto-questionnaire has been developed based on data gathered from semi-structured interviews with minority youths. This questionnaire includes items that pertain to 1) whether a child has experienced situations in which he/she perceived as being discriminated against based on ethnicity, skin color, accent, or culture. 2)the child's emotional response to the incident, and 3)the child's coping response.

The present study proposal is to administer this proto-questionnaire to a sample of minority youth between the ages of 8 and 18, and psychometrically analyze the response to determine validity and reliability of the instrument. In addition to the Perceptions of Racism questionnaire, the Revised Children's Manifest Anxiety Scale and the Child Depression Inventory will be administered (as measures to be used in the determination of construct validity). These analyses will likely result in refinement of the proto-questionnaire, which can then be used in future studies to determine the effects of racism (as a psychosocial stressor) on minority child behavioral health and development, as a contributory stressor in acute and chronic illness etiology, as well as it's effects on health care and health services issues. Initial piloting of the proto-questionnaire will be conducted at the Boys and Girls Club of Asylum Hill. Additional testing will be conducted in the Hartford Public School System (upon approval from the Superintendent's Office of the Hartford Public School System). At the Boys and Girls Club, a convenience sample of minority (i.e., African American, Puerto Rican, and West Indian/Caribbean) children attending summer camp will be recruited. In the public school system, samples based on classroom assignment in middle and high schools will be procured. In both settings, informed consent of the parent, as well as child assent will be obtained. Although general descriptive demographic information such as age and ethnicity will be obtained, anonymity and confidentiality will be maintained; no personal identifiers will be recorded. Data analyses will include factor analysis for subscale identification, item analyses, item-scale correlations, determination of the internal consistency reliability (coefficient alpha), and construct validity determination through correlation analyses.

SUBPROJECT PROGRESS:

During the present reporting period we have enrolled 53 new participants into the study. This raises our total subject number to 242 since the beginning of the project. In addition to enrolling new participants, we are transferring data from those subjects who initially were administered pencil and paper questionnaires to the web-based questionnaire that GCRC developed for the project. We will continue to recruit new subjects during the upcoming year, as well as transfer data from all paper and pencil subjects to the web system. We have not yet begun analysis of results, but plan to do so during the upcoming year.

SPID:	0633	PROTOCOL:	633	TYPE:	RESEARCH	
SHORT TITLE:	Novel 3					
LONG TITLE:	Identification of novel 3 UTR regulatory variants in candidate genes for substance dependence					
AIDS:	N	TOTALS		A	B	D
		Inpatient		0	0	0
START DATE:	5/30/2006	Scatter Bed		0	0	0
Total # pts expected for entire study:	300	Outpatient		0	0	0
		Scatter RN Hours		0	0	0
		Offsite Visits		0	0	0
RESEARCH BIONUTRITION	N	MULTICENTER STUDY		N		
INFORMATICS CORE	N	CLINICAL TRIAL		N		
BIostatistician	N	CORE LAB		Y		
ANCILLARIES ONLY	N					

INVESTIGATOR	DEPARTMENT	NON-HOST INSTITUTION: STATE, COUNTRY
JENSEN, KEVIN BS	VASCULAR BIOLOGY	
COVAULT, JONATHAN MD, PHD	Psychiatry	
FURNEAUX, HENRY M PHD	VASCULAR BIOLOGY	
KRANZLER, HENRY R MD	PSYCHIATRY	

SUBPROJECT DESCRIPTION:

The 3 untranslated region (UTR) of Messenger Ribonucleic acid (mRNA) is the major region of post-transcriptional gene regulation; however, the 3 UTRs of many genes for addictive disorders have not been extensively studied. Our interest is in gene regulation by microRNAs, a recently identified mechanism of post-transcriptional gene regulation. MicroRNAs anneal to the 3 UTR of mRNA and negatively regulate gene expression. An essential requirement of microRNA function is nucleotide base pairing to the 3 UTR of mRNA. Our hypothesis is that single nucleotide polymorphisms that occur in microRNA targets will modify gene expression and contribute to addictive disorders. Using algorithms that predict microRNA annealing to mRNA, we have successfully identified microRNA targets in the 3 UTR of the cannabinoid receptor-1 (CNR1) and serotonin receptor-1B (HTR1B) genes. These microRNA targets also contain known single nucleotide polymorphisms (SNPs) that disrupt the annealing predicted with a microRNA. Using a luciferase assay, we have shown that these SNPs release the luciferase repression conferred by the wild-type sequence. Thus these SNPs are capable of modifying gene expression. We are interested in identifying other polymorphisms that modify gene expression, and exploring their relationships with disease. However, a limitation to our current research is the lack of available 3 UTR sequence. We currently rely on SNPs deposited in The National Center for Biotechnology Information (NCBI) database, where there is often little information available on these polymorphisms, and many polymorphisms are yet to be discovered. Therefore aim 1 of this proposal is to sequence the 3 UTR of the genes encoding the GABA Receptor Alpha-2 subunit (GABRA2), the μ -opioid Receptor (OPRM1), the serotonin transporter (SLC6A4) and CNR1 in 100 controls, and 200 subjects with substance dependence. There is strong evidence to support the involvement of these genes in substance dependence. Aim 2 is to explore the prevalence of the most promising polymorphism in a larger sample. The aims proposed are consistent with our current efforts to understand microRNA regulation and human disease. Specifically, data provided by this study will support an anticipated revision for a recently submitted National Institutes of Health grant (R03), Human Variation in microRNA Target Sites and Their Relation to Addictive Disease, and will also support a National Research Service Award (NRSA) F30 submission that is planned for later this year.

SUBPROJECT PROGRESS:

Identification of novel 3 UTR regulatory variants in candidate genes for substance dependence During the course of this study, we have completed sequencing the 3'UTR of the μ -Opioid (OPRM1) and Serotonin Transporter (SLC6A4) gene in a population of approximately 280 individuals. We are currently analyzing these sequences for novel variants, and whether these variants or any other previously discovered variant might potentially modify microRNA regulation. Also as part of this study, we have utilized the high throughput SNP genotyping resources of the GCRC Core Laboratory; to explore the relationship between a polymorphism in the 3'UTR of the serotonin receptor 1b (HTR1B) and aggression related behaviors in humans. We have validated that this polymorphism moderates the regulation of microRNA, and we have found that this polymorphism correlates with aggression related behaviors. We are currently preparing this finding for publication.

SPID: 0634	PROTOCOL: 634	TYPE: RESEARCH
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SHORT TITLE:	Serotonin 1A
LONG TITLE:	Serotonin 1A Receptor and Mood in Daily Life

	AIDS:	N	TOTALS			
				A	B	D
			Inpatient	0	0	0
START DATE:			Scatter Bed	0	0	0
Total # pts expected for entire study:		1,926	Outpatient	0	0	0
			Scatter RN Hours	0	0	0
			Offsite Visits	0	0	0

RESEARCH BIONUTRITION	N	MULTICENTER STUDY	N
INFORMATICS CORE	Y	CLINICAL TRIAL	N
BIostatistician	N	CORE LAB	Y
ANCILLARIES ONLY	N		

INVESTIGATOR	DEPARTMENT	NON-HOST INSTITUTION: STATE, COUNTRY
CONNER, TAMLIN PHD	Psychiatry	
COVAULT, JONATHAN MD, PHD	Psychiatry	
KRANZLER, HENRY R MD	PSYCHIATRY	
TENNEN, HOWARD PHD	Community Medicine	

SUBPROJECT DESCRIPTION:

Recent evidence identifies variation in the gene encoding the serotonin 1A (5-HT1A) receptor (genetic locus HTR1A) as a potential factor in the development of mood and anxiety disorders, with carriers of the G allele of the C(-1019)G single nucleotide polymorphism (SNP) of HTR1A being more vulnerable to such disorders than non-carriers. We request funding to examine this allelic variation and its relation to mood-related outcomes in two existing data sets--416 Deoxyribonucleic acid (DNA) samples from college students taking part in an ongoing study of student life (IRB#03-128) and 1,510 DNA samples from a large case-control sample collected by Dr. Kranzler as part of an ongoing study of the genetics of alcohol dependence and co-morbid disorders (IRB# 96-156). The first primary aim will be to test whether variation in the HTR1A SNP predicts mood-related outcomes in the college student sample [measured by daily self-reported anxiety and other moods obtained across multiple years of study participation] and the case-control sample [measured by participants' lifetime history of Diagnostic and Statistical Manual (DSM) diagnosed major depression]. The second primary aim will be to test whether variation in HTR1A interacts with variation in the 5-HTTLPR polymorphism of the serotonin transporter gene (obtained previously in all of samples 1 and half of sample 2) to predict mood-related outcomes and lifetime history of depression. Results from primary analyses will provide pilot and feasibility data for a National Institutes of Health grant (NIH) R03 grant application by the Principal Investigator (PI) to examine the role of serotonin-related genetic predictors of mood-related experience. A secondary aim will capitalize on existing data to determine whether variation in HTR1A and its possible interaction with 5-HTTLPR predicts differences in alcohol use for the student sample and differences in alcohol dependency in the case-control sample. Results from the secondary aim will provide pilot data for the Alcohol Research Center renewal grant to be submitted in December, 2006.

SUBPROJECT PROGRESS:

This archival study involved genotyping on archived saliva samples of 416 college students. As such, no additional subjects have enrolled since the start of this project on April 1, 2006. No changes in recruitment plans were needed and no unexpected safety concerns have arisen. There have been three amendments to the protocol since its start on April 1, 2006. On January 3, 2007, the GCRC scientific advisory committee approved a no-cost extension until June 31st, 2007 to continue to analyze data. At that time, they also approved a protocol change to use remaining funds (after genotyping the original HTR1A single nucleotide polymorphism) to examine additional target SNPs in the college student sample (two Tryptophan Hydroxylase-2 gene SNPs and one SNP in the Corticotrophin Releasing Hormone Receptor 1 gene). Plans to perform genotyping on the larger case control sample (N = 1510) were removed, as primary results for HTR1A were shown to be insufficient to warrant testing in the separate sample. On March 23, 2007 approval was granted to perform genotyping on the college student sample for one additional polymorphism--the Dopamine 4 Receptor Exon 3 VNTR. All genotypes fell within guidelines of original consent provided by participants in the college study.

INTERIM DATA AND OUTCOMES (4/1/2006-3/31/2007) Serotonin Receptor 1A (HTR1A) gene The original goal of this study was to determine whether a novel polymorphism in the serotonin 1A receptor, the HTR1A c(-1019)g SNP, was related to emotional

phenotypes. This hypothesis was driven by recent data linking this gene to clinically diagnosed depression and vigilance to emotional stimuli as measured in the laboratory. The GCRC Core lab genotyped this polymorphism in the 416 archived college student saliva samples, which yielded frequencies consistent with prior work (CC 26%; CG 51%; GG 24%). I then analyzed whether genotype groups were associated with individual differences in self-reported mood states, measured daily across two 30-day time periods, each separated by one year. Primary aim 1 sought to determine whether variation in the HTR1A c(-1019)g polymorphism predicted differences in mood states. Analyses revealed no significant differences between genotype groups (cc, cg, gg) in their daily reports of sadness, hostility, anxiety or any other self-reported mood. Thus, results did not support a link between the g allele and sub-clinical differences in mood. However, exploratory analyses showed an association between this polymorphism and the degree of variability/extremity in daily mood states. Compared to the two homozygous groups (cc, gg), heterozygous individuals (cg) had greater variability in their mood states over time across both years. Such pattern of molecular heterosis has been found with this snp previously (Lesch & Canli, 2006), although not consistently. Such findings warrant replication in future daily process sets by Conner and Tennen that enable investigation of day-to-day mood variability. If patterns are replicated, this effect will warrant publication. Primary aim 2 sought to determine whether variation in the HTR1A c(-1019)g polymorphism interacted with variation in the serotonin transporter gene-linked polymorphism, 5-HTTLPR, to predict mood-related outcomes. There was some evidence of interaction, but in a direction opposite of prediction: Presence of two G alleles (gg) appeared protective in carriers of the riskier 5-HTTLPR short allele for the experience of state anxiety. Specifically, carriers of the 5-HTTLPR short allele who were also G homozygotes reported lower levels of daily anxiety that were similar to those with two copies of the protective 5-HTTLPR long allele. This pattern was replicated across two years. Because findings are contrary to predictions based on extant literature, we will await replication for this particular finding. A secondary aim was to examine whether variation in the HTR1A c(-1019)g polymorphism was related to alcohol and/or drug use. Outcomes were examined in the college student sample only. Results showed few reliable associations between the HTR1A snp and drinking/drug outcomes. Based on the above findings, the P.I. and co-investigators determined that the patterns for HTR1A were either insufficient or too inconsistent to warrant testing in the larger case control sample of 1510 individuals. Thus, we used the remaining funds to genotype four additional snps in the college student sample. Again, the primary aim was to determine whether variation in the candidate genes of interest predicted differences in daily mood states. Tryptophan Hydroxylase-2 (TPH2) gene Emerging animal and human data suggest that genetic variation in TPH2-which encodes for tryptophan hydroxylase-2, a rate-limiting enzyme in brain serotonin biosynthesis-may strongly influence brain serotonin levels, and by extension mood outcomes. Therefore, we examined the association between mood outcomes and the two most promising TPH2 polymorphisms-the G(-703)T snp (rs4570625) and the T(-473)A snp (rs11178997). Chi-square analyses revealed strong linkage between the two snps (chi-square = 182.58, $p < .001$), thus, analyses focused primarily on the more frequent G(-703)T snp. As hypothesized, carriers of the riskier T allele of the G(-703)T snp reported more intense negative mood states in their daily life, compared to those homozygous for the less risky G allele. This pattern occurred in women only. Genotype carrier status accounted for 5% of the variance in negative mood levels for women in year 1, and 3% of the variance in negative mood levels for women in year 2. Importantly, these patterns were much weaker (0.5% of variance) when examining the association with traditional self-report measures of emotion-related traits (e.g., Neuroticism). Results suggest that that daily state mood measures may be more sensitive than one-time trait measures for detecting emotion-related genetic correlates. Results are being written up for publication. Corticotropin Releasing Hormone Receptor (CRHR1) gene Emerging data also suggest that genetic variation in the corticotropin releasing hormone receptor (CRHR1) gene-which encodes for the production of adrenocorticotrophic stress hormone (ACTH) in the anterior pituitary-may influence individual differences in stress reactivity. Therefore, we examined the association between mood outcomes and the most promising CRHR1 polymorphism- rs1876831. Recent work has shown that the wild type C allele of this C to T single nucleotide polymorphism is a risk factor in binge drinking (Treutlin et al., 2006). Treutlin et al speculated that binge drinking was a result of elevated negative mood states. Thus, we hypothesized that CC individuals would report elevated negative mood states, along with elevated binge drinking levels, relative to T carriers. As hypothesized, CC individuals reported higher negative mood states in their daily life, as well less positive mood states, compared to carriers of the T allele. The effects were small but reliable. Genotype carrier status accounted for 1 and 2% of the variance in negative mood across years 1 and 2, respectively. Similar variance estimates were found for positive mood across both years. Again, as with TPH2, patterns were much weaker, and not statistically significant when examining the association with traditional self-report measures of emotion-related traits (e.g., Neuroticism; Extraversion). Unlike Treutlin, however, rs1876831 was not related to binge drinking in this college student sample. Results for the mood component will be written up for publication. Dopamine Receptor 4 (DRD4) gene Genetic differences related to dopamine function may also influence daily mood states, but in a fashion different from the serotonergic genetic differences. Specifically, dopamine may predict positive rather than negative emotion-related states, given the role of dopamine in reward circuitry (e.g., Bozarth, 1991). Thus, we are in the process of examining the most commonly studied variable number tandem repeat (VNTR) polymorphism in exon III of the D4 dopamine receptor (DRD4) as it relates to daily mood states.

Genotyping is nearly complete at the GCRC Core lab. Once genotypes are available, analyses will focus on the links between this VNTR and self-reported mood states in the college student sample. The 7 repeat allele is expected to be associated with elevated positive affective states, given prior work linking this allele to greater novelty seeking (Ebstein et al., 1996; Strobel et al., 2004), a marker of approach/reward orientation. Analyses for the DRD4 VNTR will be completed by the end of this grant-June 31st, 2007. PUBLICATIONS As of March 31st 2007, no publications have arisen from this project, although two papers are in preparation (TPH2 and CRHR1). The P.I. will cite the GCRC in the acknowledgements of all manuscripts arising from this project. REFERENCES Ebstein RP, Novick O, Umansky R, Priel B, Osher Y, Blaine D, Bennett ER, Nemanov L, Katz M, Belmaker RH.

Dopamine D4 receptor (D4DR) exon III polymorphism associated with the human personality trait of Novelty Seeking. *Nat Genet.* 1996 Jan;12(1):78-80. Lesch, K-P, Canli T. 5-HT1A receptor an anxiety-related traits: Pharmacology, genetics, and imaging. In T. Canli (Ed). *Biology of Personality and Individual Differences*; Guilford Press; NY; 2006: 273-294 Strobel A, Debener S, Anacker K, Muller J, Lesch KP, Brocke B. Dopamine D4 receptor exon III genotype influence on the auditory evoked novelty P3. *Neuroreport.* 2004 Oct 25;15(15):2411-5. Treutlein J, Kissling C, Frank J, Wiemann S, Dong L, Depner M, Saam C, Lascorz J, Soyka M, Preuss UW, Rujescu D, Skowronek MH, Rietschel M, Spanagel R, Heinz A, Laucht M, Mann K, Schumann G. Genetic association of the human corticotropin releasing hormone receptor 1 (CRHR1) with binge drinking and alcohol intake patterns in two independent samples. *Mol Psychiatry.* 2006 Jun;11(6):594-602.

SPID: 0636 **PROTOCOL:** 636 **TYPE:** RESEARCH

SHORT TITLE: Marital Interaction

LONG TITLE: Marital Interaction in Alcoholic Couples Over Time

AIDS:	N	TOTALS	A	B	D
		Inpatient	0	0	0
START DATE:	7/20/2006	Scatter Bed	0	0	0
Total # pts expected for entire study:	100	Outpatient	0	0	0
		Scatter RN Hours	0	0	0
		Offsite Visits	0	0	0

RESEARCH BIONUTRITION	N	MULTICENTER STUDY	N
INFORMATICS CORE	Y	CLINICAL TRIAL	N
BIostatistician	N	CORE LAB	N
ANCILLARIES ONLY	N		

INVESTIGATOR	DEPARTMENT	NON-HOST INSTITUTION: STATE, COUNTRY
CRANFORD, JAMES A PHD	SUBSTANCE ABUSE RESEARCH	UNIVERSITY OF MICHIGAN, MI USA

SUBPROJECT DESCRIPTION:

We are trying to determine if alcoholism leads husbands and wives to engage in more negative behaviors in marriage, and if these behaviors in turn lead to higher levels of drinking, depressed mood, marital aggression, and divorce. This project is designed to improve our understanding of several public health problems, including alcoholism, depression, marital aggression, and divorce.

SUBPROJECT PROGRESS:

This project was approved by the University of Michigan GCRC Advisory Committee on 04.27.06 (U of M GCRC File Number: 2234). This project was also approved by the University of Michigan Medical School Institutional Review Board (IRB) on 06.08.06 (study eResearch ID: HUM00001297). We obtained final approval for this study from the National Institute on Alcohol Abuse and Alcoholism on 06.20.06 (NIAAA, 1 R21 AA015105-01A2).

Upon receiving approval from the U of M GCRC Advisory Committee, the U of M Medical School IRB, and the NIAAA, we submitted a formal request to use the Interactive Voice Response (IVR) resources at the UCHC-GCRC on 07.09.06. The Scientific Advisory Committee (SAC) of the UCHC-GCRC approved our request for IVR resources on 07.24.06 (#018-06; GCRC Number 636). The UCHC IRB approved this project on 08.17.06

SPID: 0637 **PROTOCOL:** 637 **TYPE:** RESEARCH

SHORT TITLE: The DMAC Study

LONG TITLE: A Pilot study to assess the DNA Methylation patterns in Alcoholics and Controls-The DMAC Study

AIDS:	N	TOTALS	A	B	D
		Inpatient	0	0	0
START DATE:	7/18/2006	Scatter Bed	0	0	0
Total # pts expected for entire study:	96	Outpatient	38	0	0
		Scatter RN Hours	0	0	0
		Offsite Visits	0	0	0

RESEARCH BIONUTRITION	N	MULTICENTER STUDY	N
INFORMATICS CORE	N	CLINICAL TRIAL	N
BIostatistician	N	CORE LAB	Y
ANCILLARIES ONLY	N		

INVESTIGATOR	DEPARTMENT	NON-HOST INSTITUTION: STATE, COUNTRY
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HESSELBROCK, VICTOR M PHD	PSYCHIATRY	
GRAVELEY, BRENTON R PHD	GENETICS AND DEV BIOLOGY	
LALANDE, MARC MD	Genetics & Develop Biology	
LAMBRECHT, RICHARD PHD	Pharmacology & Toxicology	
THAPAR, MANISH MD	Internal Medicine	
WALSH, STEPHEN J SCD	Ctr for Biostatistics	

SUBPROJECT DESCRIPTION:

Deoxyribonucleic acid (DNA) methylation, which is thought to play an important role in carcinogenesis, is an emerging area of epigenetic research. A recent Request For Applications (RFA) (AA-06-005) from the National Institutes of Health (NIH), to which a multidisciplinary investigative group from UCHC responded (Drs. Bonkovsky, Hesselbrock, Lalande, and Lambrecht) targeted epigenetic effects of alcohol and its metabolism as an important area of research. Alcohol has long been associated with cancer and has recently been associated with increased DNA methylation levels. In this pilot study, we propose to determine whether and how DNA methylation patterns in chronic alcoholics are different from suitable controls. This will be the first step in finding out if DNA methylation patterns are altered in subjects with chronic alcohol dependence and provide important pilot data for later, larger proposals to the NIH and other external funding agencies focused on mechanisms whereby alcohol and its metabolites influence cancer risk and other epigenetic effects.

SUBPROJECT PROGRESS:

Deoxyribonucleic acid (DNA) methylation, which is thought to play an important role in carcinogenesis, is an emerging area of epigenetic research. A recent request for application (RFA) (AA-06-005) from the National Institutes of Health (NIH), to which a multidisciplinary investigative group from UCHC responded (Drs. Bonkovsky, Hesselbrock, Lalande, and Lambrecht) targeted epigenetic effects of alcohol and its metabolism as an important area of research. Alcohol has long been associated with cancer and has recently been associated with increased DNA methylation levels. In this pilot study, we propose to determine whether and how DNA methylation patterns in chronic alcoholics are different from suitable controls. This will be the first step in determining if DNA methylation patterns are altered in subjects with chronic alcohol dependence and provide important pilot data for later, larger proposals to the NIH and other external funding agencies focused on mechanisms whereby alcohol and its metabolites influence cancer risk and other epigenetic effects. Specific Aims: This pilot study is designed to obtain preliminary data on the methylation patterns of DNA for genes known or suspected of playing a role in cancer development. Aim 1: To assess global DNA methylation status in well-characterized chronic alcoholics and to compare it to suitably matched non-alcoholic family members as controls. Hypothesis 1: There are clinically and statistically significant differences in global DNA methylation and in patterns of DNA methylation in chronic alcoholics, compared to matched non-alcoholic controls. Aim 2: To explore whether there are observable, meaningful differences in methylation patterns between the two groups at different gene loci and whether there are relationships between life time alcohol use and the degree or pattern of DNA methylation. Hypothesis 2: There are differences in methylation patterns between alcoholics and controls, which correlate directly with dose and duration of alcohol use. We propose a pilot study to examine the methylation pattern in DNA samples from 48 chronic alcoholics and 48 matched controls. The field of epigenetics is the study of heritable differences related to changes in DNA expression, which are not due to differences in the DNA sequences themselves. Although still in its infancy, epigenetics is expanding rapidly. DNA methylation is one of the three main types of epigenetic inheritance. It is involved in

many physiological and pathophysiological conditions, including regulation of gene expression and silencing of repeat elements in the genome. DNA methylation plays a role in many diseases, such as multiple sclerosis, diabetes mellitus, schizophrenia, alcohol dependence, and cancer. It has been shown that global methylation status in peripheral blood monocytes (PBM) is associated with plasma homocysteine levels in healthy individuals. Chronic alcoholics commonly have elevated homocysteine levels. The importance of homocysteine to DNA methylation status stems from the fact that homocysteine is a precursor of S-adenosyl methionine (SAM), which is the methyl donor when cytosine residues in the dinucleotide sequence CpG are methylated by DNA methyltransferases (DNMT). Bonsch, et al., showed associations among alcohol-associated elevated plasma homocysteine levels, the global methylation status, and the subsequent expression of DNMT mRNAs in alcoholic patients compared to controls. These findings support the hypothesis that ethanol exposure increases DNA methylation, and suggest that changes in DNA methylation status can be responsible for changes in expression of some of the genes involved in this methylation process. Further research will be needed to confirm this possible chain of alcohol-induced events. In all likelihood, many more genes (whose levels of expression are partially controlled by the methylation status of the DNA in their promoters) are yet to be discovered. Changes in DNA methylation are recognized as one of the most common forms of molecular alteration in human neoplasia. Hypermethylation of CpG islands located in the promoter regions of tumor suppressor genes has been firmly established as a frequent mechanism for gene inactivation in cancers. In contrast, global hypomethylation of genomic DNA and loss of IGF2 imprinting were observed in tumor cells and a correlation between hypomethylation and increased gene expression was reported for many oncogenes. In addition, monitoring global changes in DNA methylation has been used for molecular classification of cancers. Most recently, gene hypermethylation was associated with clinical risk groups for neuroblastoma, as well as with hormone receptor status and response to tamoxifen in breast cancer. Therefore, it may be feasible to use methylation markers to classify and predict cancer risk, different kinds or stages of cancer, cancer therapeutic outcomes, and patient survival.

Alcoholism and cancer risk: Chronic excessive alcohol consumption is the strongest risk factor for upper aerodigestive tract (UADT) cancer (oral cavity, pharynx, hypopharynx, larynx, and esophagus). Chronic alcohol use also increases the risk for cancer of the liver, colorectum and breast. Many epidemiological studies have demonstrated a correlation between alcohol ingestion and the occurrence of cancer in these organs. Because the ingestion of all types of alcoholic beverages is associated with an increased cancer risk, more likely than not, ethanol itself is the crucial compound that increases cancer risk. The exact mechanisms of ethanol-associated carcinogenesis have remained obscure. Multiple mechanisms are believed to be involved in alcohol-associated cancer development of the UADT, including the effect of acetaldehyde (AA), the first metabolite of ethanol oxidation, induction of cytochrome P-4502E1 (CYP2E1) leading to the generation of reactive oxygen species (ROS), and enhanced procarcinogen activation, modulation of cellular regeneration, and nutritional deficiencies. Folate deficiency, primarily the consequence of low dietary intake and destruction by AA, is common in alcoholics and contributes to the inhibition of transmethylation, which is an important factor in the regulation of genes involved in carcinogenesis. Acetaldehyde decreases DNA repair mechanisms and the methylation of cytosine in DNA. However it has been shown recently that chronic alcoholics have significantly increased levels of genomic DNA methylation. About 3.6% of all cases of cancer and a similar proportion of cancer deaths are attributable to consumption of alcohol. These figures are higher in selected regions of the world, in particular in Central and Eastern Europe. Among women, 60% of cancers attributable to alcohol occur in the breast.

DNA Methylation: Methods for measurement of DNA methylation include methylation-specific enzyme digestion, bisulfite DNA sequencing, methylation-specific PCR (MSP) and MethyLight, methylation-sensitive single nucleotide primer extension (MS-SnuPE), MALDI mass spectrometry and differential methylation hybridization (DMH). However, none of these methods combines access to specific sequences in the genome with high throughput and low cost, which is needed for analyzing methylation profiles at high resolution in large sample sets. In addition, many of these methods are insensitive to low levels of methylation changes in diseased tissues, for example, 10% or 20% hypermethylation. We propose using the recently validated adaptation of a high-throughput single nucleotide polymorphism (SNP) genotyping system for DNA methylation detection, based on genotyping of bisulfite-converted genomic DNA. This technology combines a miniaturized bead-based array platform, a high level of assay multiplexing, and scalable automation for sample handling and data processing. We intend to use the technology developed by Illumina labs, including their methylation chip and bead array system. The bead array system is presently available at UConn. Illumina expects to have a fully functional assay system in the second half of this year. With use of this system, we will analyze methylation profiles of 1536 CpG sites from 371 genes. These genes were selected based upon their relevance to carcinogenesis. This assay can resolve a 22% methylation difference between samples with 99% confidence and a 10% methylation difference with 95% confidence. Resources available through the NIAAA-funded Alcohol Research Center were used to identify suitable alcohol-dependent subjects and appropriate sibling controls. This information is available as part of the database of the long-standing Collaborative Study on the Genetics of Alcoholism, (COGA). Alcohol dependent adult subjects along with their nonalcohol dependent siblings will be drawn from the COGA study sample. After being consented, 15 mL of peripheral blood will be obtained and peripheral blood monocytes (PBM) will be separated for DNA extraction using the Progene DNA purification kit and the standard protocol currently in use at the GCRC Core Lab. The plasma will be stored frozen (-80oC) in 1 mL aliquots for possible future use. The DNA samples will be stored at -80oC and processed by the Molecular Core Lab under the supervision of Dr. B. Graveley. The DNA methylation pattern will be studied using the methylation chip from Illumina labs. We will analyze the results for differences in the methylation patterns in the sibling pairs. GCRC resources have been used for recruitment and enrollment of subjects (Nursing core), for the study visits (Nursing core and exam rooms, etc), for the processing of the blood samples, including the preparation of PBM and subsequent extraction of DNA (Core laboratory). Subject recruitment has been slower than expected. To date only 29 sibling pairs have been recruited who have also provided blood samples for DNA extraction. One additional sibling pair will be completed by June 30, 2007. Following completion of this last subject pair, DNA extraction will be completed on all samples and the DNA sent to Dr Graveley's lab to examine the DNA methylation pattern using the recently available methylation

chip obtained from Illumina labs. Following a careful examination of these pilot data, papers will be written and a decision will be made whether to pursue the study hypotheses further. There have been no unexpected safety concerns from this study; no publications or presentations have resulted from this work to date.

SPID: 0639	PROTOCOL: 639	TYPE: RESEARCH
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SHORT TITLE: Pulmonary epithelial effects of hypoxia

LONG TITLE: Pilot Study of Circulating Markers of Pulmonary Epithelial Effects of Hypoxic Exposure

AIDS:	N	TOTALS	A	B	D
			Inpatient	0	0
START DATE:	9/21/2006	Scatter Bed	0	0	0
Total # pts expected for entire study:	6	Outpatient	11	0	0
		Scatter RN Hours	0	0	0
		Offsite Visits	0	0	0

RESEARCH BIONUTRITION	N	MULTICENTER STUDY	N
INFORMATICS CORE	N	CLINICAL TRIAL	N
BIostatistician	N	CORE LAB	Y
ANCILLARIES ONLY	N		

INVESTIGATOR	DEPARTMENT	NON-HOST INSTITUTION: STATE, COUNTRY
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BURKI, NAUSHERWAN K MD	Medicine/Pulmonary Medicin	
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SUBPROJECT DESCRIPTION:

Increasing evidence from in vitro animal studies suggests that hypoxia has direct cellular effects on the alveolar epithelium and the alveolocapillary membrane (1). Indirect evidence indicates that this is also likely to be true in man, but there are few studies examining this. The alveolar epithelium and pulmonary vascular endothelium perform crucial functions critical to the overall integrity of the lung, including transfer of fluid and proteins between the alveolar lumen and the interstitial and intravascular spaces, mechanical stability of the lungs, and immune and anti-inflammatory functions. In man, hypoxia-induced damage to some or all of these pulmonary functions can be inferred from some clinical syndromes, such as high altitude pulmonary edema (HAPE), but the mechanism(s) of these actions of hypoxia are unclear (2). It is well established that removal of the hypoxic stimulus relieves acute mountain sickness (3), and recent data indicate an additive effect of supplemental inhaled CO₂ with the oxygenation (4). The majority of studies on hypoxia in man have focused on ventilatory neural regulatory mechanisms (5,6,7,8,9) and autonomic nervous control of the pulmonary circulation (2); studies of possible mechanisms of hypoxia-induced lung damage in man have, of necessity been invasive, such as analysis of bronchoalveolar lavage fluid, which itself may alter the milieu being studied (10) and invasive vascular studies (11). There have been no studies specifically evaluating the effects of hypoxia on the pulmonary epithelium in man, partly because until recently there were no available, generally accepted circulating biomarkers of pulmonary epithelial function. Clara cell protein (CC16) is expressed in pulmonary Clara cells and has been shown in animal (12) and human studies (13) to be a sensitive marker of pulmonary epithelial function. Circulating levels of CC16 are altered on exposure to ozone or other noxious stimuli (14, 15). In order to investigate the effects of hypoxia, we performed studies on circulating markers of pulmonary epithelial and endothelial function in normal subjects exposed to hypoxia at sea level and identified changes in circulating levels of these markers. Our hypothesis is that exposure to hypoxia in normal human subjects directly affects pulmonary epithelial and endothelial cell function; in its severe form this may be manifested as pulmonary edema. This effect of hypoxia may be modified by mucosal acidification as would occur with an increase in alveolar CO₂.

SUBPROJECT PROGRESS:

We studied six healthy, normal volunteers: valid data were obtained in 5 subjects (Age range 28 - 43 yrs; 3 male and 2 female). Each subject was studied on two separate occasions. On each occasion, the subject was seated in a comfortable armchair and a venous cannula was inserted in a forearm vein. A pulse oximeter probe and electrocardiograph leads were attached for continuous monitoring of arterial O₂ saturation (SaO₂), heart rate and electrocardiographic pattern. The subject was then asked to breathe through a one-way valve via a mouth piece. Minute ventilation and end-tidal CO₂ were recorded while the subject breathed room air, and a baseline blood sample was taken from the venous cannula. The inspiratory side of the valve was then attached to a Douglas bag containing either room air (control day) or a gas mixture of 11% O₂, balance N₂ (experimental day). The subject breathed this mixture for 30 minutes and then returned to or continued room air breathing and was disconnected from the apparatus.

SaO₂ decreased from a baseline of 99.4% to 78.6% during hypoxic exposure. Blood samples were drawn at baseline, after 30 mins of hypoxic gas mixture breathing, and at 1, 2, and 4 hours after return to normoxic room air breathing. Samples were immediately spun and the serum frozen at -70°C, pending analysis.

CC16 was measured in the samples by a latex immunoassay technique using polyclonal antibody (43). Adhesion molecules (i.e. VCAM, E-Selectin, L-Selectin, ICAM-1) were measured in plasma using standard commercially available ELISA kits (R&D Systems,

Minneapolis, MN). No significant changes were noted in circulating adhesion molecules either on the control day or following exposure to hypoxia. During the control day there was a steady decline in CC16 over 4 hours, similar to findings reported previously. In all subjects the circulating CC16 fell ($p < 0.05$) after 30 mins of hypoxia (SaO₂ 78.6%±2.6%) and then returned to baseline at 1 hr; it then gradually declined over the next 4 hours. Serum CC 16 levels, ng/ml. Baseline: Control = 7.32±12.04, Hypoxia = 7.25±12.78; 30 min: Control = 7.24±11.97, Hypoxia = 6.56±12.06*; 60 min: 6.97±11.78, Hypoxia = 7.25±12.78; 120min: Control = 6.77±12.4, Hypoxia = 6.89±11.4; 240min: Control = 6.54±11.69, Hypoxia = 6.79±11.21. * = signif change from baseline, $p < 0.05$.

These results show that short term acute hypoxia results in activation of pulmonary Clara cells with no significant effect on circulating adhesion molecules. These data suggest that acute hypoxic exposure in man results in effects on the pulmonary epithelium but not on the pulmonary vascular endothelium.

SPID: 0640 **PROTOCOL:** 640 **TYPE:** RESEARCH

SHORT TITLE: Tonsillar Cancer**LONG TITLE:** Prevalence of Human Papillomavirus in Tonsillar Cancer and Age Matched Diseases Free Controls

AIDS:	N	TOTALS	A	B	D
		Inpatient	0	0	0
START DATE:	10/19/2006	Scatter Bed	0	0	0
Total # pts expected for entire study:	75	Outpatient	0	0	0
		Scatter RN Hours	0	0	0
		Offsite Visits	0	0	0

RESEARCH BIONUTRITION	N	MULTICENTER STUDY	N
INFORMATICS CORE	Y	CLINICAL TRIAL	N
BIostatistician	Y	CORE LAB	N
ANCILLARIES ONLY	N		

INVESTIGATOR	DEPARTMENT	NON-HOST INSTITUTION: STATE, COUNTRY
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SPIRO, JEFFREY MD	Surgery	
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SUBPROJECT DESCRIPTION:

We hypothesize that 33% of the tonsillar squamous cell carcinoma tissue analyzed will have evidence of a virulent strain of Human Papilloma Virus (HPV) (16, 18, 31, 33). Within this subgroup of subjects the response to therapy measured in 5 year survival data will be greater than the remaining 2/3rd. We also expect that the tonsillar specimens of healthy non-cancerous patients will be free of virulent strains of HPV. This would allow for a stronger argument of causation rather than association. To look for an increase in HPV for those patients who have no other risk factors.

SUBPROJECT PROGRESS:

During this retrospective study 48 tonsillar specimens and 40 age matched controls were evaluated. The tissue was processed with in situ hybridization using a high risk human papilloma virus (HPV) probe. At this time we have no plans to add additional subjects to the study. We will continue to follow the current subjects that are still alive. There were no identified safety concerns. We found 35% of our tonsillar tissue had HPV integration. With 36 month follow up as our cutoff criteria we found a trend towards better outcome in the HPV + population. With another year or two of follow up we hope to see that trend become significant. In our analysis a greater portion of HPV + patients had to be kept out since they didn't reach the 36 months Follow-up mark. Morphologically we found that HPV + tumors arose significantly more from the crypt epithelium rather than the surface epithelium (and HPV - arose more from the surface epithelium.). A possible next step would be to look at the immune cross talk between tumor and host and compare to HPV status.

No publications have been submitted at this time. In the next couple of months as the manuscript is prepared it is our intent to cite the GCRC.

We are indebted to this program which has allowed us to carry out this study to date. We hope that as we develop further studies off of this foundational research the GCRC will be willing and able to support our efforts. Submitted by Adam Luginbuhl, MD (Research Coordinator)

SPID: 0641	PROTOCOL: 641	TYPE: RESEARCH
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SHORT TITLE:	Stressors
LONG TITLE:	Mental and Physical Stressors in the Diagnosis of Breast Cancer. A multidisciplinary analysis of distress and systemic biomarkers in patients referred for biopsy of a suspected breast cancer lesion

AIDS:	N	TOTALS	A	B	D
		Inpatient	0	0	0
START DATE:	12/21/2006	Scatter Bed	0	0	0
Total # pts expected for entire study:	100	Outpatient	0	0	0
		Scatter RN Hours	0	0	0
		Offsite Visits	0	0	0

RESEARCH BIONUTRITION	N	MULTICENTER STUDY	N
INFORMATICS CORE	Y	CLINICAL TRIAL	N
BIostatistician	N	CORE LAB	Y
ANCILLARIES ONLY	N		

INVESTIGATOR	DEPARTMENT	NON-HOST INSTITUTION: STATE, COUNTRY
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TANNENBAUM, SUSAN MD	Medicine/Hem-Onc	
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SUBPROJECT DESCRIPTION:

Women begin to face their greatest fear when they have been told that their routine mammogram or breast exam is abnormal. Women experience an array of symptoms throughout the course of their diagnosis, treatment and recovery from breast cancer. Symptoms are perceived indicators of change in normal functioning as experienced by patients. Symptoms disrupt daily functioning, most notably social function and communication. Symptom outcomes impact functional and emotional status, health care service utilization, mortality/morbidity, financial status, and self-care/management. Research has demonstrated the presence of significant associations between symptoms experienced by breast cancer survivors, suggesting a complex web of symptom experience. The nature of the complex interactions between symptoms remains unclear. Patients with one symptom are likely to have others, as well. Cancer-related fatigue, depressive-anxiety symptoms and sleep disturbances are the most frequent symptoms experienced by women diagnosed with breast cancer. These symptoms can have a devastating impact on their quality of life. Recent studies imply a correlation of these symptoms with selected markers of inflammation including levels of proinflammatory cytokines.

Systemic Biomarkers: Biomarkers like carcinoembryonic antigen, CA-125 and prostate-specific antigen (PSA) are helpful in monitoring and in some cases diagnosing cancer (41). Three new serum biomarkers derived from membrane proteins found on breast cancer cells, Aminopeptidase N (CD13), membrane type 1-matrix metalloproteinase (MT1-MMP), and stromal derived receptor-1 (SDR-1), are hopeful novel biomarkers that may prove useful in the diagnosis of breast cancer. Aminopeptidase N, also known as CD13, is a membrane-bound, zinc-dependent peptidase that cleaves neutral amino acids from the N terminus of oligopeptides. In addition to being expressed by a number of tissues, CD13 is aberrantly upregulated on both the tumor cells and developing blood vessels of cancerous tissue. Accumulating evidence points to CD13 as a key regulator in this tissue of both angiogenesis, or new blood vessel formation (42, 43), and the migration and invasion of tumor cells (44, 45). Interestingly, although CD13 was first defined as a membrane bound protein, a soluble form was later detected in a variety of bodily fluids including blood. Moreover, a number of studies have shown CD13 to be elevated in the serum of cancer patients, and to correlate with larger tumor size (46, 47). To date, however, no studies have investigated CD13 serum activity as a prognostic marker. Membrane type 1-matrix metalloproteinase (MT1-MMP) also shares similar characteristics as CD13. It is expressed as an inactive cell surface proteinase which is induced under breast cancer progression and angiogenic responses (48-50). Interestingly, the functional activation of MT1-MMP results in increased cell migration and invasion and has been shown to be actively translocated to the cell surface in hypoxia, both in vitro and in human breast cancer (51). It has also been shown to be shed from tumors as an active fragment which can be detected by MT1-MMP-specific fluorescent peptide substrates (52, 53). The third biomarker is a novel cell surface protein which is over-expressed in human breast cancer and is selective for a highly invasive ductal carcinoma; high expression predicts distant metastasis (54). This cell surface protein also depicts cleaved protein isoforms in human breast tumor lysates indicating it may be shed in blood. This novel tumor antigen was identified from a breast cancer patients sentinel lymph node and an antibody directed against it was synthesized. This unique antibody will be used in a fluorescent-based assay on blood samples to determine whether it is a potential diagnostic marker.

SUBPROJECT PROGRESS:

10 patients enrolled and 19 screened to date. No changes in recruitment plans. No unexpected safety concerns. No data available at this

time. No changes to the protocol. No publications to date.

SPID: 0642	PROTOCOL: 642	TYPE: RESEARCH
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SHORT TITLE: PACTG 1047

LONG TITLE: Pediatric Aids Clinical Trials Group (PACTG) 1047: Version 1-Phase II Safety and Immunogenicity Study of Quadrivalent Human Papillomavirus [Types 6, 11, 16, 18] L1 Virus-Like Particle [VLP] Vaccine (Gardasil®) in HIV-Infected Children > 7 to < 12 Yea

AIDS:	Y	TOTALS	A	B	D
		Inpatient	0	0	0
START DATE:	11/16/2006	Scatter Bed	0	0	0
Total # pts expected for entire study:	1	Outpatient	2	0	0
		Scatter RN Hours	0	0	0
		Offsite Visits	0	0	0

RESEARCH BIONUTRITION	N	MULTICENTER STUDY	Y	
INFORMATICS CORE	Y	CLINICAL TRIAL	Y	Phase II
BIostatistician	N	CORE LAB	N	
ANCILLARIES ONLY	N			

INVESTIGATOR	DEPARTMENT	NON-HOST INSTITUTION: STATE, COUNTRY
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SALAZAR, JUAN C MD	PEDIATRICS	
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SUBPROJECT DESCRIPTION:

Pediatric Aids Clinical Trials Group (PACTG) 1047 is a phase II, double blind, placebo controlled study of the safety and immunogenicity of Quadrivalent Human Papilloma virus (QHPV) vaccine in a population of Human Immunodeficiency Virus (HIV)-1 infected boys and girls aged 7 years to under 12 years. The vaccine, also known as Gardasil was developed by Merck Labs with the target viral types being 6, 11, 16, and 18. The most common oncogenic Human Papillomavirus (HPV) types that cause cervical dysplasia and cancer, in both HIV-infected and uninfected women, are HPV 16 and 18. The most common types of HPV, causing genital warts, are types 6 and 11. On May 18, 2006, an advisory committee for the Federal Drug Administration (FDA) reviewed Merck's application for licensure of Gardasil®. It is expected that the vaccine will receive approval in early June, 2006. However, no HIV-infected children, or children with other immune compromising conditions, have been enrolled or received monovalent or quadrivalent HPV vaccine in any clinical trials.

The incidence of cervical cancer in HIV-infected women increases as immune competence decreases with progression of HIV disease. Cervical cancer is more extensive and more difficult to cure in HIV-infected women than in HIV-uninfected women and the recurrence rate after standard clinical care is higher. In addition, HIV-infected individuals are at increased risk for penile and anal cancer, including individuals who do not report prior anal intercourse. Because HPV is a sexually transmitted infection, prevention in women will be enhanced by prevention in their partners as well. Thus, evaluation of a prophylactic vaccine, which might protect HIV-infected girls and boys from infection with the most common HPV types that cause anogenital dysplasia and external genital lesions, is an important scientific goal.

The study population will consist of 120 HIV-1 infected children recruited from multiple PACTG sites in the U.S. This protocol will be undertaken in children > 7 to < 12 years of age because it is likely that this preventative vaccine will be used before children become sexually active. It is expected that, in terms of safety, QHPV Vaccine will be generally well-tolerated in HIV-infected children in this age group. The subjects will be randomly selected to receive the study vaccine or placebo, with 75% receiving the active vaccine and 25% receiving placebo during Stage I of the study. Since it is expected that children with weaker immune status would respond differently from children with stronger immune systems, the population will be stratified into three groups based on their CD4% history and current CD4%.

Stage I: After satisfying eligibility criteria including real-time pregnancy testing for menstruating females, the vaccine/placebo is given intramuscularly 3 times (at entry, week 8 and week 24). Subsequent safety assessment consists of at least 30 minutes in the clinic directly after immunization, a day 3 phone evaluation, study visits on week 4, 8, 12, 24, and 28. Subjects will also be asked to keep a record of oral temperature and symptoms following the injections. (See attached Appendix IV, the Vaccination Report Card) Subjects will be strongly encouraged to phone the study nurse or Dr. Salazar should any unusual or alarming symptoms occur.

Stage II: At week 96, the groups will be unblinded. If the vaccine has been deemed safe and well tolerated, a fourth dose will be given to those children who had received active QHPV. The placebo group would now begin the regimen of active QHPV and follow up visits. For the group who receives the fourth dose of active QHPV, safety follow up will occur at weeks 97, 100 and

108. Those who begin active QHPV at 96 weeks will be followed in a likewise fashion until study week 124. (Please see attached Appendix 11 A and IB.) Throughout the course of the study, immunogenicity will be evaluated via blood and saliva samples using ELISPOT (anti-HPV CMI), HPV antibody cLIA (Competitive Luminex Immunoassay) and IgG and IgA anti-HPV testing.

SUBPROJECT PROGRESS:

Pediatric Aids Clinical Trials Group (PACTG) 1047 (Version 1.0) has had one enrollment in the reporting period. Due to funding changes throughout the PACTG/IMPAACT Network, our site was unable to enroll any more subjects to the protocol as on November 2006.

Letter of Amendment 2 was issued to clarify the following items

1. Pregnancy Testing may be performed on either blood or urine samples. This was also clarified in the informed consent.
2. Vaccine preparation- the pharmacist should not prepare the vaccine ahead of time, nor should the vaccine be left at room temperature longer than 15 minutes nor should the vaccine be stored in the syringe. Pharmacists must document the time the vaccine was drawn up in the syringe and the time the vaccine was removed from the refrigerator. If the temperature of the vaccine or the refrigerator or the placebo falls below 2 degrees C., the pharmacist should not use the material and contact the protocol pharmacist.

The informed consent was also amended to change the terminology from HPV-infected to HPV -susceptible in the Benefits section.

The full follow-up schedule for this study extends past our sites funding capacity. And because this is a blinded, placebo controlled study, our site is awaiting guidance from the protocol chair regarding continued follow-up for our subject.

SPID: 0643 **PROTOCOL:** 643 **TYPE:** RESEARCH

SHORT TITLE: HITEC
LONG TITLE: Health Improvement Through Training and Employee Control (HITEC)

AIDS:	N	TOTALS	A	B	D
		Inpatient	0	0	0
START DATE:	11/16/2006	Scatter Bed	0	0	0
Total # pts expected for entire study:	600	Outpatient	0	0	0
		Scatter RN Hours	0	0	0
		Offsite Visits	0	0	0

RESEARCH BIONUTRITION	N	MULTICENTER STUDY	N
INFORMATICS CORE	N	CLINICAL TRIAL	N
BIostatistician	Y	CORE LAB	N
ANCILLARIES ONLY	N		

INVESTIGATOR	DEPARTMENT	NON-HOST INSTITUTION: STATE, COUNTRY
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CHERNIACK, MARTIN G MD	OCCUPATIONAL/ENVIRONME NTAL	
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SUBPROJECT DESCRIPTION:

This study compares two different approaches to combining workplace safety and health with personal health improvement. The primary focus is on improvement of musculoskeletal health (mobility and fitness, preventing and controlling joint disease, and workplace risk reduction), and the secondary focus is on depression and mental health. One approach relies on traditional health promotion, where a management sponsored program offers an educational package and professional review of work organization and ergonomics. The second approach involves developing groups within the workforce (Employee Sponsored Groups or ESPs) that will determine and construct workplace health and safety and personal health programs. The study involves a comparison of costs, measures of health status, and evaluation of the effectiveness of the workforce planning groups. The direct involvement of the workers compensation insurance carrier in the study team is intended to produce realistic and respected agreements about health program conduct and content between the workforce and management. There is a significant economic and econometric component, which is designed to link health and process outcomes to rate structure.

SUBPROJECT PROGRESS:

1 U19 OH008857-01 Center for Promoting Health in the New England Workplace: Project B (HITEC) Project Year 1: (July 1, 2006-June 30, 2007) Personnel: Jeffrey Dussetschleger, DDS, MPH joined the project as a Research Assistant/Study Manager. He began work on 9/1/06. AIMS: Because of the reduced budget, we elected to stagger Project B and defer full activities until January 1, 2007. For the first 6 months of the fiscal year, there was a skeleton operation consisting of preliminary work on constructing goniometric data loggers, and preliminary site selection in cooperation with Travelers' staff. Project Aims for Project Year 1 (7/1/06-6/30/07) and current status are listed in the following table (target date and status in parenthesis). 1. Select sites within next 6 mths, in order to begin site prep. Work (12/31/06; in progress, 4 sites selected and withdrawn). 2. Formalize actual travel costs, and finalize a resource use estimate (3/31/07; pending final site selection). 3. Revise study design, as needed, to accommodate issues around workforce size, division of single production site, etc. (3/31/07; pending final site selection). 4. Determine availability and suitability of GCRC resources, especially for expanded field effort (9/30/06; completed, GCRC application acted on). 5. Produce working exposure data loggers and integrated exposure approach (PATH) by 4th Quarter of Year I (6/30/07; circuitry completed, on target). 6. Complete slide show for Travelers personnel (10/15/06; completed and in use). 7. Identify site team, including Travelers, to work with Supriya Lahiri on baseline site information. Be prepared to begin site evaluation on accelerated basis, following site selection (1/1/07; economic and econometric CDMT functioning). 8. Make final determination on feasibility of a mid-point assessment (3/31/07; completed). 9. Purchase instruments and supplies for exposure monitoring (11/30/06; completed). 10. Establish written protocol and data collection forms for subject testing (4/30/07; pending). 11. Through biometrics CDMT, analyze responses on Project A questionnaire and determine suitable components of survey (12/31/06; completed). 12. Prepare generic questionnaire (minus site specific questions) for HITEC (2/28/07; completed). 13. Add site specific questions (3/31/07; pending site selection). 14. Begin Pre-testing of Survey Instrument (5/15/07; in progress). 15. Prepare version 1.0 of Study manual (10/31/06; completed). 16. Submit final questionnaire and data collection forms to Institutional Review Board (IRB) (6/30/07; in progress). 17. Complete data base on questionnaire validation and repeated measures use (9/30/06; completed). 18. Recommendation from CDMT on health promotion package for Standard of Care (SOC) sites (3/31/07; phase 1 completed, phase 2 in progress). 19. Hire and/or submit work plan for graduate student assistants (10/31/06; completed). In general, targets have been met, but with still important delays in site selection. A description follows.

Clarification of Status in Specific Program Areas Site Selection: The study team and a 12-member Travelers working group named Health Promotion and Behavior on the Workplace have met monthly throughout the year. A 36 item scaled survey tool was jointly designed to screen 1200 corporate clients as possible sites. This was completed by the appropriate claims account executive (CAE). Fourteen sites were identified.

This was reduced to 8 because of imminent contract negotiations. The list was reduced to 2 national market companies (sites) with facilities in Connecticut and Long Island. Detailed slide shows and project books were developed for the CAE's, underwriters, and brokers. Materials were individualized to each site. The two companies had each indicated a strong interest in an onsite WHP program. Discussions and presentations proceeded from November 2006-March 2007. In addition, a detailed time allocation profile was completed at the site level, providing for all estimated staff and workforce time.

This was a reductive strategy concentrating on finalization of "best sites." Unfortunately, in the past month both companies have declined to continue participation. While cited reasons may not accurately capture intent, one firm was extremely enthusiastic but was advised against participation by the corporate legal department because of concerns over liability. The second firm cited a recent large decline in stock price and the need to focus on internal affairs. These outcomes were unexpected and disappointing to the Travelers group and the study team. We are proceeding with a different recruitment strategy. Travelers will hold an employers school before the end of May 2007. Screening criteria will be relaxed and employers will attend voluntarily rather than be selected. Travelers has also opened its non-public corporation list for review. So far, three additional candidate firms have been identified. We have also begun discussions with 3 national companies with regional facilities that are self-insured and not Travelers clients. We have also begun discussion with another insurer about sites. We have also begun regular discussions with State of Connecticut public services worker representatives and Commissioners about state sites. This would also involve a non-Travelers site and introduce new issues specific to the public sector workforce. We will advise the National Institute for Occupational Safety and Health (NIOSH) of any design changes that will be required by new site addition. Even if non-Travelers sites are included, we are insisting on Travelers continued involvement, although there will be new protocols for de-identifying data. Questionnaire Development: There has been extensive questionnaire refinement and editing. Changes to date have relied heavily on responses from Project A. In the original application, we had indicated likely inclusion of the SF-12 CES-D, JCQ, ERI, Frone' work-family conflict, Q-DASH, Qualitative Social Support, Perceived Stress, adapted NCOD, and internally used questions. In the current iteration, the job content questionnaire (JCQ) has been expanded to include work organization questions, the full SF-36 has been adopted to better assess well-being, and Health Locus of Control and Health Self-Efficacy questions have been added. The latter is in review, given ambiguous responses in Project A. There is, in addition, an added SES component. The questionnaire is complete with the exception of a decision on adding a dietary battery. The final version will be site specific, but we are currently in the process of focus group evaluation for acceptability. An additional question involves method of administration. In the original proposal, we had planned for Staff Preparation and Training: Because focus groups and qualitative methods figure prominently in HITEC, staff attended all-day training sessions in qualitative methods with Professor David Morgan of Portland State University on 10/17/06 and with Mr. Ray Maietta of Research Talk, Inc. on use of qualitative software on 2/23/07. The economics and econometrics methods team has developed a basic cross-project variable list which was reviewed and approved in a group meeting on 2/23/07. Development of Exposure Monitors: Data Logging The HITEC project includes a plan to monitor musculoskeletal exposure by direct data logging. Over the first year of the project, a functioning circuit and sensor have been designed and tested for evaluating joint movement. In the original research plan, modifications of existing devices for long-duration data-logging were proposed. The proposed system was based on a robust field device designed to monitor grip force and vibration. However, the existing technology, when modified to monitor electro-goniometric sensors instead of acceleration sensors, appeared to introduce electronic limitations that significantly compromised the integrity of the captured signals. As a result, a new high-speed data collection system, designed specifically for electro-goniometric measurements, was constructed. The new system uses a PIC digital signal processor that is integrated with a 10-channel, 12-bit analog-to-digital (A/D) converter system operating at clock rate of 2 kHz. Two-dimensional joint displacements of the neck, shoulders, and wrists over an entire workday are represented by waveforms collected from five bi-axial electro-goniometric sensors. Waveform data, preserved in binary file format for file size reduction, are directly written to a high-speed 2 GB SD memory card that is formatted in the standard FAT32 file system and is readable by any Windows-based operating system. A MatLAB interface has been designed to convert the binary waveforms into its decimal voltage equivalents and to facilitate data manipulation and analysis with minimal user input. A single electro-goniometric sensor typically has a low relative sensitivity of 10 microvolts/supply voltage/degree and requires a gain of 400 within the custom system in order to properly extend the sensor signal into the A/D converter range; however, the gain has been observed to greatly increase noise levels in laboratory testing. Precision signal conditioning, via hardware electronics, has been developed and the system demonstrates a repeated ability to resolve angles to within a half a degree of accuracy, which is an improvement on similar published research. The prototype system is being expanded to include all 10 channels and laboratory testing will continue to validate electronic performance, power duration, and signal integrity. Upon the successful completion of these tests, the electronic layout of the prototype system will be used to develop a printed circuit board from which the final field devices will be constructed. Under the current timeline, we expect to have at least 5 fully operational systems tested and usable when we enter the field. There has, however, been one additional change. The electrogoniometers are from a sole source manufacturer. Since the grant application was submitted, the only available device was "upgraded" at a 500% increase in cost. We have shifted funds from other projects to produce the minimum number of units. Unfortunately, the steep reductions in the NIOSH final budget preclude more extensive device manufacturing.

Evaluation Plan: In the original proposal, a 5-dimension survey was presented for ongoing evaluation: D1) Employee knowledge base:

the degree to which an employee perceives that there is an identifiable level of health knowledge within the organization that can be drawn on to help improve health and wellbeing. D2) Employee involvement: the degree to which employees perceive that they can actively affect decisions in their environment as they apply to health promotion. D3) Employee support: the degree to which employees are willing to be involved in the health promotion program as well as to follow-through with the implementation of solutions generated through the program. D4) Managerial support: the degree to which employees perceive that both line-managers and upper management have a genuine and supporting interest in promoting health through the implementation of workplace and program changes. D5) Employee stress: stress felt by employees caused by changes to the workplace related to the program. The short length of the survey instrument (17 items) enables repeated use to track the effectiveness of the participatory program over time and then to make timely changes in a targeted and iterative fashion. Survey results are applicable to evaluation of ESP program effectiveness. Because the study team has yet to enter the field, the evaluation instrument has been in the development phase. This has involved three components. 1) A checklist available across projects to assess level of worksite organizational readiness 2) A multi-domain checklist to assess company resources, programs, and policies 3) A schedule and format for qualitative evaluation to augment surveys In addition, as part of CPH-NEW, a semi-annual executive committee was held on 1-19-07 where the HITEC project was presented and reviewed for compliance with aims and objectives. Summary of Findings Although there are no study results to date, there has been activity around two of the Aims - Aim 2 and Aim 4. 2. Development of evaluation processes sufficient to compare outcomes from ESP programs to a more traditional wellness and ergonomic programs: the standard of care (SOC). 4. Direct participation of the insurance carrier in quantifying costs and benefits, in developing a rate-based incentive structure, in "institutionalizing" the employer's involvement, and in disseminating results. New and specific evaluation processes have been in development and involve three areas: survey assessment, qualitative assessment and cost assessment. Regarding survey design, we have been analyzing the Pro-Care responses to health self-efficacy and stages of change questions, and found overstated linked responses to various lifestyle questions, such as intent to lose weight, exercise, restrict fats, etc. Discrepancies between expressed goals and self-assessment have caused the biometrics methods team to question the accuracy and utility of these types of sequential questions. Accordingly, we are currently evaluating and pre-testing alternatives including hedonic scale metrics or eliminating groups of questions. From the perspective of qualitative methods, the study team has developed a preliminary schedule and table of contents for focus group-based evaluation. We have also prepared a multi-year time allocation frame for relevant personnel time. Finally, there have been regularly scheduled discussions on modeling "avoided costs" and expanding productivity measures. This is important but still under conceptual development. The involvement of insurance underwriters in the process has clarified cost quantization. Mid-market target firms carry their own medical and indemnity costs up to a self-insured threshold. Worker's compensation premiums increasingly do not reflect these actual costs. A different situation prevails in group health. This has lead to the view that for candidate companies, worker's compensation directs costs and premiums are not a sufficient motivation to support most health promotion and intensive workplace prevention interventions. Thus, the issue changes to productivity measures such as employee retention, premature morbidity or health-induced retirement or group health costs. Thus, based on observations to date on claims volumes of candidate companies and actual costs, the institutionalization of "incentivization" will probably require development of new metrics.

SPID: 0644 **PROTOCOL:** 644 **TYPE:** RESEARCH

SHORT TITLE: Anastrozole
LONG TITLE: Effect of Anastrozole on Bone Turnover Markers and Bone Mineral Density in Postmenopausal Women with Primary Breast Cancer: A Pilot Study

AIDS:	N	TOTALS	A	B	D
		Inpatient	0	0	0
START DATE:	11/16/2006	Scatter Bed	0	0	0
Total # pts expected for entire study:	25	Outpatient	0	0	0
		Scatter RN Hours	0	0	0
		Offsite Visits	0	0	0

RESEARCH BIONUTRITION	N	MULTICENTER STUDY	N
INFORMATICS CORE	Y	CLINICAL TRIAL	N
BIostatistician	N	CORE LAB	N
ANCILLARIES ONLY	N		

INVESTIGATOR	DEPARTMENT	NON-HOST INSTITUTION: STATE, COUNTRY
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TAXEL, PAMELA MD	Medicine	
TANNENBAUM, SUSAN MD	Medicine/Hem-Onc	

SUBPROJECT DESCRIPTION:

Aromatase Inhibitors (AI) are effective for secondary prevention of breast cancer and may soon replace tamoxifen as first-line therapy in the treatment of hormone-sensitive breast cancer. However, because these medications produce a marked reduction in serum estrogen levels, this is likely to result in an increased rate of bone loss and risk of developing osteoporosis and fractures in postmenopausal women treated with these agents. Indeed, substantial bone loss has been reported in several large clinical trials of AIs. Osteoporosis drugs are available that could prevent this loss, but they have frequent side effects and are expensive. Thus, treating all women receiving AIs might not be the most appropriate and cost-effective approach. A better approach might be to select women at highest risk of bone loss and only treat them with antiresorptive agents. We hypothesize that women who demonstrate high bone turnover, as reflected by markers which can be measured in blood and urine samples in the first 3 to 6-months on treatment, will have greater bone loss.

The proposed pilot study will evaluate women who receive anastrozole therapy, are receiving adequate amounts of calcium and vitamin D and have baseline normal or moderately low bone mass in order to determine if early changes in bone turnover markers correlate with bone loss at one year. If data from this pilot protocol support our hypothesis, then we would propose a larger trial to confirm it. The ultimate aim is to predict which women are at higher risk of bone loss and therefore treat them earlier with bone-sparing agents, while those with lower risk could be monitored on conservative therapy.

SUBPROJECT PROGRESS:

This study has recently begun enrollment. We have 3 subjects to screen for enrollment, and have a recent advertising campaign to help recruit more volunteers.

PUBLICATIONS: JOURNALS

+Authored by CAP/MCAP, *CRC Personnel

SPIDs PMID Published	Cited	Reference
0486 16928887	Y	Alarcon-Chaidez F, Ryan R, Wikel S, Dardick K, Lawler C, Foppa IM, Tomas P, Cushman A, Hsieh A, Spielman A, Bouchard KR, Dias F, Aslanzadeh J, Krause PJ. Confirmation of tick bite by detection of antibody to Ixodes calreticulinsalivary protein. <i>Clin Vaccine Immunol</i> . 2006 Nov;13(11):1217-22. Epub 2006 Aug 23.
0157 16387451	Y	Arias A, Feinn R, Kranzler HR. Association of an Asn40Asp (A118G) polymorphism in the mu-opioid receptor gene with substance dependence: a meta-analysis. <i>Drug Alcohol Depend</i> 83 262-8 2006.
0495, 0117 16756424	Y	+Armeli S, Feinn R, Tennen H, Kranzler HR. The effects of naltrexone on alcohol consumption and affect reactivity to daily interpersonal events among heavy drinkers. <i>Exp Clin Psychopharmacol</i> . 2006 May;14(2):199-208.
0442 17101320	Y	Bonkovsky HL, Naishadham D, Lambrecht RW, Chung RT, Hoefs JC, Nash SR, Rogers TE, Banner BF, Sterling RK, Donovan JA, Fontana RJ, Di Bisceglie AM, Ghany MG, Morishima C, HALT-C Trial Group. Roles of iron and HFE mutations on severity and response to therapy during retreatment of advanced chronic hepatitis C. <i>Gastroenterology</i> 131 1440-51 2006.
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0161 16759340	N	Dahl JP, Cubells JF, Ray R, Weller AE, Lohoff FW, Ferraro TN, Oslin DW, Kampman KM, Dackis C, Tang Y, Gelernter J, Kranzler HR, O'Brien CP, Berrettini WH. Analysis of variations in the tryptophan hydroxylase-2 (TPH2) gene in cocaine dependence. <i>Addict Biol</i> 11 76-83 2006.
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0051 16792556	Y	Dick DM, Plunkett J, Wetherill LF, Xuei X, Goate A, Hesselbrock V, Schuckit M, Crowe R, Edenberg HJ, Foroud T. Association between GABRA1 and drinking behaviors in the collaborative study on the genetics of alcoholism sample. <i>Alcohol Clin Exp Res</i> 30 1101-10 2006.
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0442 17133499	Y	Everson GT, Hoefs JC, Seeff LB, Bonkovsky HL, Naishadham D, Shiffman ML, Kahn JA, Lok AS, Di Bisceglie AM, Lee WM, Dienstag JL, Ghany MG, Morishima C, HALT-C Trial Group. Impact of disease severity on outcome of antiviral therapy for chronic hepatitis C: Lessons from the HALT-C trial. <i>Hepatology</i> 44 1675-84 2006.
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0340, 0357 17081504	Y	Gelernter J, Panhuysen C, Weiss R, Brady K, Poling J, Krauthammer M, Farrer L, Kranzler HR. Genomewide linkage scan for nicotine dependence: identification of a chromosome 5 risk locus. <i>Biol Psychiatry</i> . 2007 Jan 1;61(1):119-26. Epub 2006 Nov 1.
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In Press

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- 0468 Y Zuo L, Kranzler HR, Luo X, Covault J, Gelernter J CNR1 variation modulates risk for drug and alcohol dependence Biological Psychiatry.

SOURCE OF INVESTIGATORS' SUPPORT

FOUNDATION

SOURCE	GRANT/CONTRACT	FUNDS	SPID
ALBERTSEN, PETER			
CTRC RESEARCH FOUNDATION		12,280	0365
KAMINER, YIFRAH			
DONAGHUE FOUNDATION		120,000	0629
KENNY, ANNE M			
DONAGHUE FOUNDATION		110,000	0614, 0617
DONAGHUE FOUNDATION		130,550	0624
ONCKEN, CHERYL			
DONAGHUE FOUNDATION		118,973	0598
WINOKUR, ANDREW			
SUSAN G KOMEN BREAST CANCER FOUNDATION		44,250	0601
	FOUNDATION	\$536,053	

INDUSTRY

SOURCE	GRANT/CONTRACT	FUNDS	SPID
BONKOVSKY, HERBERT L			
ZYMENEX A/S (FORMERLY HEME BIOTECH A/S)		79,594	0505
KELLY, JOHN R			
H RAUTER GMBH & CO KG		198,258	0558
KURTZMAN, SCOTT			
Z-TECH INC		59,717	
	INDUSTRY	\$337,569	

PVAS

SOURCE	GRANT/CONTRACT	FUNDS	SPID
TANNENBAUM, SUSAN			
CT BREAST HEALTH INITIATIVE INC		50,000	0641
TAXEL, PAMELA			
CT BREAST HEALTH INITIATIVE INC		64,790	0644
WAGNER, JULIE			
AMERICAN DIABETES ASSOCIATION		100,000	0453
AMERICAN HEART ASSOCIATION		65,000	0591
	PVAS	\$279,790	

OTHER NON FEDERAL

SOURCE	GRANT/CONTRACT	FUNDS	SPID
ABU-HASABALLAH, KHAMIS			
UCONN-STORRS		11,347	0605
YALE UNIVERSITY		2,245	0622
BONA, ROBERT			
WORCESTER MEMORIAL HOSPITAL		13,000	0268
CHERNIACK, MARTIN G			
UMASS LOWELL		273,141	0643
CLOUTIER, MICHELLE M			
BRIGHAM & WOMEN'S HOSPITAL		129,865	0337, 0626
CT CHILDREN'S MEDICAL CENTER		27,356	0337, 0626
DIECKHAUS, KEVIN			
UCONN-STORRS		13,314	0581
HESELBROCK, VICTOR M			

SUNY - BROOKLYN	710,351	0051
KENNY, ANNE M		
YALE UNIVERSITY	198,228	
KRANZLER, HENRY R		
YALE UNIVERSITY	191,402	0468
YALE UNIVERSITY	50,000	0340
YALE UNIVERSITY	229,817	0357
KURTZMAN, SCOTT		
UNIV OF PITTSBURGH	19,900	0290
UNIV OF PITTSBURGH	60,850	0279, 0282, 0286, 0329, 0372, 0374, 0399, 0400, 0428, 0506, 0575, 0576, 0577, 0578
ONCKEN, CHERYL		
DUKE UNIVERSITY	32,444	0466
SALAZAR, JUAN C		
UMASS	138,471	0500, 0502, 0540, 0566, 0567, 0585, 0621, 0642
TENNEN, HOWARD		
UCONN-STORRS	10,295	0605
WAGNER, JULIE		
UCONN-STORRS	6,241	0628
OTHER NON FEDERAL	\$2,118,267	

FEDERAL

SOURCE	GRANT/CONTRACT	FUNDS	SPID
Federal - PHS			
ARMELI, STEPHEN R			
NIH	5R21AA015691-02	0	
NIH	7R21AA015691-03	144,538	
ARNOLD, ANDREW			
NIH	5R01CA055909-13	290,000	
ASELTINE, ROBERT H			
NIH	5R21AA015123-02	144,408	0554
ASTUR, ROBERT S			
NIH	5R21DA020013-02	141,132	
BABOR, THOMAS F			
NIH	5R01AA015383-02	322,420	
NIH	5R01DA016592-03	405,101	
NIH	5R21AA014635-03	132,153	
NIH	5R01DA018949-03	543,603	
BARTA, WILLIAM D			
NIH	5R21AA015665-02	168,605	0605
BAUER, LANCE D			
NIH	5R01DA017666-02	328,986	0599
NIH	2T32AA007290-26	7,128	
BONKOVSKY, HERBERT L			
NIH	5U01DK065193-04	174,000	0551, 0562
NIH	5R01DK038825-21	385,940	
CALHOUN, VINCE D			

NIH	5R01EB005846-02	90,655	
NIH	5R01EB000840-04	170,152	
CARROLL, KATHLEEN M			
NIH	5R01DA019078-02	344,342	
NIH	4R37DA015969-05	315,901	
NIH	5U10DA013038-07	1,250,000	
NIH	3U10DA013038-06S1	190,000	
NIH	5K05DA000457-07	127,235	
CHERNIACK, MARTIN G			
CDC	3U01OH007312-05S1	34,773	0643
CLOUTIER, MICHELLE M			
NIH	5R01HL070785-05	662,013	0337, 0626
COONEY, NED L			
NIH	5R01AA011197-08	456,168	0538
COVAULT, JONATHAN			
NIH	1R01AA015606-01A1	427,693	0612, 0620
CRANFORD, JAMES A			
NIH	1R21AA015105-01A2	218,620	0636
DANNENBERG, ANDREW J			
NIH	5R01CA082578-05	274,710	0487
DONGARI-BAGTZOGLOU, ANNA I			
NIH	5R01DE013986-06	318,584	0526
NIH	5R21DE016466-02	181,250	0572
FISHER, JEFFREY D			
NIH	5R01MH066684-04	1,084,443	0581
NIH	1R01MH077524-01A1	947,496	
FORD, JULIAN D			
NIH	5K23MH001889-05	175,694	
FORTINSKY, RICHARD H			
NIH	5R01NR005081-06	266,432	
FRANK, MARION E			
NIH	5R01DC004849-05	267,137	0596
NIH	3R01DC004099-06A2S	14,500	
	1		
NIH	2R01DC004099-06A2	442,329	
FREILICH, MARTIN A			
NIH	1R01DE017873-01	562,303	
NIH	5K23DE014187-05	123,188	0336
FRIEDLAND, GERALD H			
NIH	3U01AI046347-05S2	534,147	0426
NIH	3U01AI046347-05S1	802,493	0426
FURNEAUX, HENRY M			
NIH	1R03DA022226-01	148,000	0633
GELERNTER, JOEL E			
NIH	5R01DA012690-07	1,039,374	0357
NIH	3R01DA012849-05S1	289,903	0340
NIH	5D43TW006166-05	317,807	
NIH	5R01AA011330-08	705,574	
NIH	2R01DA012849-06A2	868,941	0340
NIH	5K24DA015105-04	90,215	
GRAVELEY, BRENTON R			
NIH	5R01GM067842-04	269,026	
NIH	2R01GM062516-06A1	384,748	

HESELBROCK, VICTOR M			
NIH	5P50AA003510-30	1,706,726	
HLA, TIMOTHY T			
NIH	5P01HL070694-05	1,903,366	
NIH	5R01HL049094-14	338,916	
NIH	2R37HL067330-06	370,000	
NIH	5R01CA095181-05	315,043	
KADDEN, RONALD M			
NIH	2R01DA012728-06A2	501,945	0364
KAMINER, YIFRAH			
NIH	5K24AA013442-05	100,882	0629
NIH	5R01AA012187-05	360,293	0629
KENNY, ANNE M			
NIH	5R01AG018887-05	290,000	0410
NIH	3R01AG018887-05S1	74,694	0410
KING, ANDREA C			
NIH	5R03AA015337-02	74,946	0563
NIH	5R01DA016834-02	627,452	
NIH	5R01AA013746-04	335,062	
KRANZLER, HENRY R			
NIH	5K24AA013736-05	135,778	
NIH	5R01AA013631-04	285,320	0531
NIH	1R01DA018432-01A2	844,939	0340
KUCHEL, GEORGE A			
CDC	1R01CI000319-01	347,200	
LALLA, RAJESH V			
NIH	5K23DE016946-02	132,126	0487
LI, ZIHAI			
NIH	5R01CA100191-03	232,212	
LITT, MARK D			
NIH	5R01AA012827-05	411,679	0446
NIH	5R21AA014202-03	140,331	0589
NIH	5R01DE014607-04	305,390	0497
LORENZO, JOSEPH A			
NIH	5P30AR046026-05	575,899	
NIH	5R01AR048714-04	237,800	
NIH	1R13AR053808-01	17,000	
MARKS, LAWRENCE E			
NIH	1G20RR019640-01A1	292,820	
NIH	5R01DC006688-03	293,243	0596
MAYER, BRUCE J			
NIH	5R01CA082258-08	318,584	0445, 0455, 0477
NIH	5R33CA107785-03	451,292	0445, 0455, 0477
MCELHANEY, JANET E			
NIH	5R01AI068265-06	418,738	0524
MEYER, JOHN D			
CDC	5R21OH008543-02	179,450	0590
CDC	5T01OH008612-02	147,592	
MOHLER, WILLIAM A			
NIH	5R01HD043156-05	277,125	
MUKHERJI, BIJAY			
NIH	5R01CA088059-05	210,613	0439

NIH	5R01CA117254-02	255,082	
ONCKEN, CHERYL			
NIH	5R01DA015167-05	274,632	0466, 0538
PACHTER, LEE M			
NIH	5K23HD040348-05	107,488	0632
PEARLSON, GODFREY D			
NIH	5R01AA015615-02	235,907	
NIH	3R37MH043775-15S1	76,850	
NIH	5R37MH043775-15	359,352	
NIH	1R01DA020709-01A1	412,264	
PETRY, NANCY M			
NIH	5R01DA016855-04	352,926	
NIH	5R01DA018883-03	478,463	0446, 0519
NIH	5R01MH060417-08	466,947	
NIH	5R01DA013444-06	449,170	0613
NIH	5R01DA014618-04	359,800	0469
PILBEAM, CAROL C			
NIH	2R01AR047673-05A2	325,600	
NIH	5R01DK048361-12	323,093	
RADOLF, JUSTIN D			
NIH	5R37AI026756-19	353,981	
NIH	5R01AI029735-16	427,441	
NIH	5R01AI038894-10	384,588	0292
RAISZ, LAWRENCE G			
NIH	5R01AR018063-30	322,123	0303, 0413
RAJAN, THIRUCHANDURAI V			
NIH	5R01AI050228-05	362,500	
NIH	2R56AI039075-10	346,865	
NIH	5R01AI039075-09	430,200	
ROSSOMANDO, EDWARD F			
NIH	5R25DE016281-03	149,999	
ROUNSAVILLE, BRUCE J			
NIH	5K12DA000167-15	816,293	
NIH	3R01DA015477-04S1	40,589	
NIH	5K05DA000089-23	126,360	
NIH	5R01DA005626-18	410,402	
NIH	5P50DA009241-13	1,990,745	
NIH	5R01DA015477-04	346,289	
SALAZAR, JUAN C			
NIH	5K23AI062439-02	150,820	
SARFARAZI, MANSOOR			
NIH	2R01EY011095-11A1	516,049	
NIH	5R01EY014959-03	318,584	0494
SCHENSUL, JEAN			
NIH	3R01DA014863-05S1	85,635	0627
NIH	3R01DA014863-05S2	34,020	
NIH	5R01DA014863-05	606,573	
NIH	5R21AA014803-02	375,469	
SECOR, ERIC R			
NIH	5F32AT001569-03	62,336	
SPIELMAN, ANDREW			
NIH	5R01AI052284-04	400,365	
SRIVASTAVA, PRAMOD K			

NIH	5R01CA084479-07	309,344	0534
STEINBERG, KAREN L			
NIH	5K23HD001477-05	118,978	
STEVENS, MICHAEL C			
NIH	5K23MH070036-03	159,697	
SULLIVAN, TAMI P			
NIH	5K23DA019561-02	162,319	0622
TAYLOR, ROBERT E			
NIH	5P20AA014643-04	1,267,101	
NIH	3P20AA014643-04S2	14,800	
NIH	3P20AA014643-04S1	76,771	
NIH	5G12RR003048-19	1,282,667	
NIH	5M01RR010284-12	2,285,551	
TELFORD, SAM R			
NIH	5R01AI064218-02	314,300	
THRALL, ROGER S			
NIH	5R01AI043573-07	314,327	
WARFIELD, SIMON K			
NIH	1R03CA126466-01A1	70,750	
NIH	5R21MH067054-02	152,415	
NIH	1R01RR021885-01A1	338,000	
WIKEL, STEPHEN			
NIH	5R01AI062735-03	283,185	0496
WOLFSON, LESLIE			
NIH	5R01AG022092-03	615,929	0582
	Federal - PHS	<u>\$52,140,250</u>	
	FEDERAL	\$52,140,250	
TOTAL FUNDING:		\$55,411,929	

RESOURCE SUMMARY: SUBPROJECTS

The following only includes information associated with subprojects.

	Pilot (CReFF)	Research	Core Inf.	Total
Number of Subprojects	0	165	0	165
Number of Investigators	0	207	0	207
Number of Published	0	51	0	51
Number of In Press	0	10	0	10
Subprojects Using	A	B	D	
Inpatient Days	0	0	0	
Scatter Bed Days	0	0	0	
Outpatient Visits	5,296	209	0	
Scatter RN Hours	63	0	0	
Offsite Research Visits	5,796	16	0	
Subprojects Using	Total SPID Count			
Patient Days/Visits	95			
Research Bionutrition	0			
Informatics Core	97			
Biostatistician	38			
Ancillaries Only	0			
Multicenter	58			
Clinical Trial	44			
Core Lab	63			

RESOURCE SUMMARY: ADMINISTRATIVE**GCRC Personnel Function**

Program Direction	0.500
Administration	2.400
Nutrition and dietary support	0.000
Bioinformatics, computer systems managers	2.100
Biostatistician	0.800
Nursing	9.500
Research Subproject Advocacy	1.200
Core lab staff	4.000
Other	1.100
Total FTEs:	21.600

INVESTIGATORS**On Subprojects****Not On Subprojects**

Clinical Investigators	207	9
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GEOGRAPHICAL USAGE BY INVESTIGATORS AT NON-HOST INSTITUTIONS

Subproject Investigators by Country	1
CANADA	1
USA Subproject Investigators by State	55
CT	39
DC	4
IL	2
MA	6
MI	1
NC	1
NJ	1
NY	1

CLINICAL INVESTIGATORS BY DEGREE

PHD Only	72
PHD and MD	9
PHD and Dental	1
PHD and Other Doctoral	0
MD Only	108
MD and Other Doctoral	0
Dental Only	13
Educator Only	0
Other Doctoral Only	4
NON-Doctoral ONLY	17
NO DEGREE	0

RESOURCE SUMMARY: PUBLICATION/SUPPORT**PUBLICATIONS**

	Published		In Press	
	Cited	Total	Cited	Total
Journals	49	58	12	13

INVESTIGATOR SUPPORT**NON-FEDERAL**

FOUNDATION	\$536,053
INDUSTRY	\$337,569
OTHER	\$2,118,267
PVAS	\$279,790

NON-FEDERAL	<u>3,271,679</u>
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FEDERAL**PHS**

AA	\$8,248,372
AG	\$980,623
AI	\$5,523,950
AR	\$1,478,422
AT	\$62,336
CA	\$2,727,630
CDC	\$709,015
DA	\$15,003,549
DC	\$1,017,209
DE	\$1,772,840
DK	\$883,033
EB	\$260,807
EY	\$834,633
GM	\$653,774
HD	\$503,591
HL	\$3,274,295
MH	\$3,422,894
NR	\$266,432
RR	\$4,199,038
TW	\$317,807

PHS	<u>52,140,250</u>
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TOTAL SUPPORT	<u><u>\$55,411,929</u></u>
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CENSUS DATA (for A, B, C, and D Patients)**Age Census Inpatient**

Age Group	ADMISSIONS			INPATIENT DAYS		
	A	B	D	A	B	D
a. less than 1 year	0	0	0	0	0	0
b. 1 thru 12 years	0	0	0	0	0	0
c. 13 thru 21 years	0	0	0	0	0	0
d. 22 thru 65 years	0	0	0	0	0	0
e. 66 and over	0	0	0	0	0	0
Total	0	0	0	0	0	0

Age Census Scatter Bed

Age Group	ADMISSIONS			INPATIENT DAYS		
	A	B	D	A	B	D
a. less than 1 year	0	0	0	0	0	0
b. 1 thru 12 years	0	0	0	0	0	0
c. 13 thru 21 years	0	0	0	0	0	0
d. 22 thru 65 years	0	0	0	0	0	0
e. 66 and over	0	0	0	0	0	0
Total	0	0	0	0	0	0

Age Census Outpatient

Age Group	OUTPATIENT VISITS		
	A	B	D
a. less than 1 year	0	0	0
b. 1 thru 12 years	122	7	0
c. 13 thru 21 years	520	0	0
d. 22 thru 65 years	3,659	139	0
e. 66 and over	995	63	0
Total	5,296	209	0

Age Census Offsite

Age Group	OFFSITE RESEARCH VISITS	
	A	B
a. less than 1 year	0	0
b. 1 thru 12 years	66	0
c. 13 thru 21 years	246	0
d. 22 thru 65 years	5,483	12
e. 66 and over	1	4
Total	5,796	16

Utilization Table

Funding Category	INPATIENT		SCATTER BED		OUTPATIENT	
	Awarded	Used	Awarded	Used	Awarded	Used
A	0	0	0	0	0	5,296
B	0	0	0	0	0	209
C	0	0	0	0	0	0
D	0	0	0	0	0	0

Outpatient

Length of Stay (hrs)	OUTPATIENT VISITS				OFFSITE VISITS	
	A	B	C	D	A	B
a. < 1 hour	4,511	195	0	0	5,796	16
b. >= 1 and <= 3	640	8	0	0	0	0
c. > 3 and <= 6	68	6	0	0	0	0
d. > 6 and <= 10	5	0	0	0	0	0
e. > 10 hours	72	0	0	0	0	0
Total	5,296	209	0	0	5,796	16

GCRC Capacity**Number**

Total Inpatient Beds	0
Inpatient Beds Used for Outpatients	0
Outpatient Rooms	9

PATIENT CARE COMPUTATION: (Figures to be rounded to nearest dollar)

RATE 1

INPATIENT

1.	If proposed rate is used, show date filed with HHS:					
2.	If rate has been published by HHS, show date of agreement:					
3.	Period applicable rate:	4/1/2006	through	6/30/2006		
4.A.	Routine Cost (or Space Cost for Per Diem Method):					0
4.B.	Per Diem Method:	0	Category A days x \$	0.00	=	0
4.C.	Scatter Beds:	0	Category A days x \$	0.00	=	0
	Total (4A and 4B and 4C)					\$0
5.	Service Patient Credit (routine method):					
	0	Category B days x \$	0.00	=	0	
	0	Category C days x \$	0.00	=	0	
	0	Category D days x \$	0.00	=	0	
5.A.	Total Service Patient Credits					0
5.B.	All Other Inpatient Credits (specify: grants, contracts, other sources)					0
	Total Credits (5A and 5B)					\$0
6.	Inpatient Ancillaries Required Solely for Research Purposes, Adjusted to Cost (Schedule 1)					
	0	Category A days x \$	0.00	=	0.00	
	0	Category B days x \$	0.00	=	0.00	
	0	Scatter Bed A days x \$	0.00	=	0.00	
	0	Scatter Bed B days x \$	0.00	=	0.00	
	Total Inpatient Ancillaries					\$0
7.	Other Costs (Specify: Drugs, raw food, special diets, outside laboratories, etc. provide Justification)					\$0
8.	Total Inpatient Charges (Lines 4, 6 and 7, less 5)					\$0
OUTPATIENT						
9.	Space Charge					\$0
10.	Outpatient Ancilla					
	1,069	Category A Visits x \$	17.17	=	18,351.94	
	71	Category B Visits x \$	0.00	=	0.00	
	Total Outpatient Ancillaries					\$18,352
11.	Other Costs (Specify: drugs, raw food, special diets, outside laboratories, facility fees, etc. Provide justification)					\$17,581
12.	Outpatient Credits:					
	0	Category B Visits x \$	10.00	=	0	
	0	Category C Visits x \$	10.00	=	0	
	0	Category D Visits x \$	10.00	=	0	
12.A.	Total Outpatient Credits					\$0
12.B.	All Other Outpatient Credits (specify: grants, contracts, other sources)					\$0
	Total Credits (12A and 12B)					\$0
13.	Total Outpatient Charges (Lines 9, 10, and 11, less line 12)					\$35,933
14.	Total Ancillary Costs Connected with Ancillary-Only Projects					\$0
15.	Total Ancillary Costs Connected with Offsite Research Visits					\$0
	TOTAL PATIENT CARE CHARGES (Lines 8 + 13 + 14)					\$35,933

RATE 2

INPATIENT

1.	If proposed rate is used, show date filed with HHS:					
2.	If rate has been published by HHS, show date of agreement:					
3.	Period applicable rate:	7/1/2006	through	3/31/2007		
4.A.	Routine Cost (or Space Cost for Per Diem Method):					0
4.B.	Per Diem Method:	0	Category A days x \$	0.00	=	0
4.C.	Scatter Beds:	0	Category A days x \$	0.00	=	0
	Total (4A and 4B and 4C)					\$0
5.	Service Patient Credit (routine method):					
	0	Category B days x \$	0.00	=	0	
	0	Category C days x \$	0.00	=	0	
	0	Category D days x \$	0.00	=	0	
5.A.	Total Service Patient Credits					0
5.B.	All Other Inpatient Credits (specify: grants, contracts, other sources)					0
	Total Credits (5A and 5B)					\$0
6.	Inpatient Ancillaries Required Solely for Research Purposes, Adjusted to Cost (Schedule 1)					
	0	Category A days x \$	0.00	=	0.00	
	0	Category B days x \$	0.00	=	0.00	
	0	Scatter Bed A days x \$	0.00	=	0.00	
	0	Scatter Bed B days x \$	0.00	=	0.00	
	Total Inpatient Ancillaries					\$0
7.	Other Costs (Specify: Drugs, raw food, special diets, outside laboratories, etc. provide Justification)					\$0
8.	Total Inpatient Charges (Lines 4, 6 and 7, less 5)					\$0
OUTPATIENT						
9.	Space Charge					\$0
10.	Outpatient Ancilla					
	4,227	Category A Visits x \$	7.50	=	31,690.42	
	138	Category B Visits x \$	0.34	=	47.22	
	Total Outpatient Ancillaries					\$31,738
11.	Other Costs (Specify: drugs, raw food, special diets, outside laboratories, facility fees, etc. Provide justification)					\$61,343
12.	Outpatient Credits:					
	138	Category B Visits x \$	10.00	=	1,380	
	0	Category C Visits x \$	10.00	=	0	
	0	Category D Visits x \$	10.00	=	0	
12.A.	Total Outpatient Credits					\$1,380
12.B.	All Other Outpatient Credits (specify: grants, contracts, other sources)					\$0
	Total Credits (12A and 12B)					(\$1,380)
13.	Total Outpatient Charges (Lines 9, 10, and 11, less line 12)					\$91,700
14.	Total Ancillary Costs Connected with Ancillary-Only Projects					\$0
15.	Total Ancillary Costs Connected with Offsite Research Visits					\$0
	TOTAL PATIENT CARE CHARGES (Lines 8 + 13 + 14)					\$91,700

4/1/2006 6/30/2006

OTHER COSTS DURING YEAR

Itemized costs. These totals appear on line 7 (Inpatient Other Costs) and on line 11 (Outpatient Other Costs) of the Patient Care Computation sheet.

<u>DRUGS, RAW FOOD, SPECIAL DIETS, LABS, ETC.</u>	<u>INPATIENT</u>	<u>OUTPATIENT</u>
John Dempsey Hospital - Patient Nutrition	0.00	265.40
John Dempsey Hospital - investigational pharmacy	0.00	4,717.16
Medical/Dental Supplies	0.00	8,982.02
Outside lab - Esoterix	0.00	697.60
Outside lab - Yale University	0.00	2,436.00
Outside lab - Yankee Dental Arts	0.00	483.00
Grand Total:	0.00	17,581.18

7/1/2006 3/31/2007

OTHER COSTS DURING YEAR

Itemized costs. These totals appear on line 7 (Inpatient Other Costs) and on line 11 (Outpatient Other Costs) of the Patient Care Computation sheet.

<u>DRUGS, RAW FOOD, SPECIAL DIETS, LABS, ETC.</u>	<u>INPATIENT</u>	<u>OUTPATIENT</u>
John Dempsey Hospital - Investigational Pharmacy	0.00	18,868.64
John Dempsey Hospital - Patient Nutrition	0.00	1,061.60
Medical/Dental Supplies	0.00	26,946.07
Outside lab - Esoterix	0.00	2,790.40
Outside lab - Yale University	0.00	9,744.00
Outside lab - Yankee Dental Arts	0.00	1,932.00
Grand Total:	0.00	61,342.71

INPATIENT

1. If proposed rate is used, show date filed with HHS:
2. If rate has been published by HHS, show date of agreement:
3. Period applicable rate: 04/01/2006 through 06/30/2006
- 4.A. Routine Cost (or Space Cost for Per Diem Method): 0
- 4.B. Per Diem Method: 0 Category A days 0
- 4.C. Scatter Beds: 0 Category A days 0
- Total (4A and 4B and 4C) \$0
5. Service Patient Credit (routine method):
- 5.A. Total Service Patient Credits 0
- 5.B. All Other Inpatient Credits (specify: grants, contracts, other sources) 0
- Total Credits (5A and 5B) \$0
6. Inpatient Ancillaries Required Solely for Research Purposes, Adjusted to Cost (Schedule 1)

0	Category A days	0
0	Category B days	0
0	Scatter Bed A days	0
0	Scatter Bed B days	0

 Total Inpatient Ancillaries \$0
7. Other Costs (Specify: Drugs, raw food, special diets, outside laboratories, etc. provide Justification) \$0
8. Total Inpatient Charges (Lines 4, 6 and 7, less 5) \$0

 OUTPATIENT

				\$0
9.	Space Charge			
10.	Outpatient Ancillaries Required Solely for Research Purposes, Adjusted to Cost (Schedule 2)			
	5,296 Category A Visits		50,042	
	209 Category B Visits		47	
	Total Outpatient Ancillaries			\$50,090
11.	Other Costs (Specify: drugs, raw food, special diets, outside laboratories, facility fees, etc. Provide justification)			\$78,924
12.	Outpatient Credits:			
	138 Category B Visits		1,380	
	0 Category C Visits		0	
	0 Category D Visits		0	
12.A.	Total Outpatient Credits			\$1,380
12.B.	All Other Outpatient Credits (specify: grants, contracts, other sources)			\$0
	Total Credits (12A and 12B)			\$(1,380)
13.	Total Outpatient Charges (Lines 9, 10, and 11, less line 12)			\$127,633
14.	Total Ancillary Costs Connected with Ancillary-Only Projects			0
15.	Total Ancillary Costs Connected with Outpatient Research Visits			0
<hr/>				
TOTAL PATIENT CARE CHARGES (Lines 8 + 13 + 14)				\$127,633

ANCILLARY CHARGES REQUIRED FOR RESEARCH PURPOSES

Department/ Cost Center

INPATIENT

Gross Charges

Adjustment
Factor (%)

Net Charges

A

B

A

B

TOTAL

Department/ Cost Center

OUTPATIENT

Gross Charges

Adjustment
Factor (%)

Net Charges

A

B

Factor (%)

A

B

Rate Period: 4/1/2006-6/30/2006

Clinical Lab

31,089.71

0.00

34.50%

10,725.95

0.00

Radiology - Diagnostic

12,304.00

0.00

58.30%

7,173.23

0.00

Vascular Lab

701.95

0.00

64.50%

452.76

0.00

TOTAL

44,095.66

0.00

18,351.94

0.00

Rate Period: 7/1/2006-3/31/2007

Clinical Lab

75,873.41

33.00

34.00%

25,796.96

11.22

Professional Fees

2,270.00

45.00

80.00%

1,816.00

36.00

Radiology - Diagnostic

306.00

0.00

55.70%

170.44

0.00

Research DXA

2,397.00

0.00

100.00%

2,397.00

0.00

Vascular Lab

1,764.04

0.00

85.60%

1,510.02

0.00

TOTAL

82,610.45

78.00

31,690.42

47.22

CORE LABORATORY

Test Name	# of Tests	# of SPIDS	SPIDS
25 OH Vitamin D	417	4	0588, 0557, 0410, 0413
Androstenediol Glucuronide	191	1	0620
Bone Specific Alkaline Phosphatase	436	4	0433, 0557, 0410, 0413
CD40 Ligand	32	1	0582
Clara Cell 16	56	1	0639
Cortisol	195	1	0557
Creatinine	179	2	0433, 0410
DHEA-S	374	3	0588, 0557, 0410
Dihydrotestosterone	191	1	0620
DNA Extraction	2,852	26	0625, 0536, 0492, 0495, 0494, 0497, 0453, 0340, 0357, 0637, 0599, 0600, 0602, 0518, 0560, 0620, 0630, 0466, 0611, 0612, 0468, 0413, 0231, 0471, 0478, 0531
DPD	179	2	0433, 0410
E-Selectin	92	2	0639, 0568
Estradiol	378	3	0433, 0557, 0410
Estrone	194	1	0557
Facs analysis	69	2	0461, 0608
Genotyping	20,281	14	0625, 0634, 0536, 0492, 0633, 0549, 0600, 0602, 0560, 0620, 0466, 0612, 0471, 0478
Growth Hormone	195	1	0557
hsCRP	135	3	0582, 0606, 0572
ICAM-1	88	2	0582, 0639
IGF-I	195	1	0557
IL-1b	36	1	0568
IL-6	127	2	0582, 0572
Insulin	32	1	0582
I-PTH	357	3	0588, 0557, 0410
Leptin	8	1	0606
L-Selectin	56	1	0639
Lyme	261	1	0496
MCP-1	32	1	0582
NTX	373	3	0433, 0557, 0410
Osteocalcin	503	4	0433, 0557, 0410, 0413
PBMC	63	2	0624, 0600
PINP	184	2	0433, 0410
pSelectin	32	1	0582
RNA Extraction	169	4	0637, 0461, 0600, 0572
RT-PCR	2,678	4	0600, 0292, 0572, 0530

Sample Processing	14,393	53	0535, 0582, 0624, 0536, 0487, 0492, 0495, 0590, 0426, 0433, 0494, 0497, 0542, 0591, 0442, 0453, 0340, 0551, 0357, 0628, 0637, 0599, 0461, 0600, 0557, 0601, 0268, 0562, 0639, 0602, 0518, 0606, 0620, 0630, 0466, 0641, 0611, 0523, 0568, 0612, 0614, 0051, 0410, 0468, 0528, 0572, 0413, 0417, 0529, 0231, 0471, 0478, 0531
Sequencing	555	3	0625, 0633, 0530
SHBG	286	4	0433, 0557, 0410, 0413
Testosterone	476	4	0433, 0557, 0410, 0413
Thrombin-Antithrombin Complex	36	1	0568
Tissue Factor	36	1	0568
TNFa	36	1	0568
VCAM	56	1	0639
VEGF	36	1	0568

MINORITY/CLINICAL ASSOCIATE PHYSICIAN PROGRAM SUMMARY

Current Status of CAPS whose appointments terminated in the last 5 years.

	Teaching	Clinical Research	Basic Research	Clinical Practice	Other
ONCKEN, CHERYL Administrative	10	89	0	0	1
SILVERMAN, DAVID	5	5	0	90	0
TAXEL, PAMELA Administrative	8	25	0	33	34

Current Appointment and Address of Previous CAPS

ONCKEN, CHERYL

Current Appoint:

Current Address: University of Connecticut Health Center
Hypertension/Medicine, MC-3940
263 Farmington Avenue
Farmington, CT 06030

Phone Number: 860-679-3425

SILVERMAN, DAVID

Current Appoint:

Current Address: University of Connecticut Health Center
Calhoun Cardiology Center, MC-2202
263 Farmington Avenue
Farmington, CT 06030

Phone Number: 860-679-2771

TAXEL, PAMELA

Current Appoint:

Current Address: University of Connecticut Health Center Endocrinology/Medicine,
MC-5456
263 Farmington Avenue
Farmington, CT 06030

Phone Number: 860-679-4743

MEDICAL STUDENTS

The University of Connecticut School of Medicine has a Medical Student Summer Fellowship Program through the Office of Medical Student Affairs. The students formally apply to that program. Applications are reviewed by the Program Director and the Associate Dean for Medical or Dental Affairs and selection is based on available faculty sponsorship. All applicants with clinical projects meet with the GCRC Program Director. The Program Director presents all potential applicants' projects to the Scientific Advisory Committee. The SAC selects the applicants with the most relevant GCRC projects and ensures that a clinical investigator is available as a mentor. All applicants are required to attend an present at a weekly seminar series with the GCRC Associate Program Director for Education and Planning. All applicants are required to present their work at a Medical Student Research Day at the end of the summer.

Students and their Mentors.

ARMSTRONG, AMY

Degree Sought	MD, BS
Mentor Name	COVAULT, JONATHAN
Period	06/01/2006 - 08/31/2006
Funds Received	3,000 *
Project Title	Genetic Study of Two Alcohol Dependence Related Genes Encoding Alpha-2 and Gamma-1 Subunits
SPIDS	0549, 0549
Project Summary	This summer I worked on two different but related projects. In the first, a continuation of my research from last summer, I studied the effects of early life stress and maternal behavior on GABA receptor subtype prevalence in rat brain tissue. This year I included female rats and studied both glucocorticoid mRNA levels as well as GABA receptor subtypes. My second project, which used human DNA, involved sequencing the GABA(A) gamma-1 receptor promoter region in alcoholics versus controls to identify functional variants linked to alcohol dependence associated "snp18."

CARTER, WILLIAM

Degree Sought	MD, BS
Mentor Name	TRAPE, MARCIA
Period	06/01/2006 - 08/31/2006
Funds Received	3,000 *
Project Title	Analyses of Occupational Injuries and Implementation of Preventive Strategies at Connecticut Tobacco Farms
SPIDS	

Project Summary

Background: Migrant farm workers (MFW) beliefs about risk factors for adverse health conditions do not correlate with scientific evidence, suggesting lack of awareness of risks experienced in the fields. Focus groups and in depth personal interviews have been shown to be effective methods to obtain qualitative valid information about MFW knowledge, beliefs and practices. This project goals were: 1) to gain a better understanding of the health knowledge and attitudes, behaviors, and exposures which influence CT MFW health and 2) to select health-related knowledge and behavioral gaps to be addressed during educational activities.

Methods: MFW clinic visits data gathered by the MassLeague from 2000-2005 were grouped based on ICD-9 and analyzed. Two MFW focus groups (N=15) and individual surveys with quizzes (N=34) were performed at a farm to evaluate understanding of the training provided.

Results: The MassLeague data showed greater percentage of all potentially occupational-related diagnoses, with trends seen over the planting and harvesting months, during high farming activity months. The selected diagnoses were not significantly different from other diagnoses identified during UCONN Students' Primary Care Clinics at the farms but differed significantly from all remaining farms from the MassLeague data set. The interviews demonstrated that few MFW had ever received pesticide training. Training with pictures was more effective than without them.

Conclusions: Lack of knowledge causes some illness promoting behaviors. To increase MFW knowledge the use of pictorial educational materials was shown to be effective. Further studies are needed to evaluate interventional methods and generalizability of results.

This abstract has been submitted for presentation at the 2007 APHA Annual Meeting. Will made presentations at the Annual International Unite for Sight meeting in Stanford, CA this past spring.

During this 2007 summer, Will is planning to continue with this project to evaluate the effectiveness of educational interventions addressing some of the major issues identified during last year's focus groups and surveys: 1) sun exposure risk and 2) pesticides risks. This will be done using a case-control model in at least 2 farms with one with education about sun exposure prevention and risks. The other one, with education on pesticides health effects prevention and risks. Pre and post intervention surveys will be used to measure improvement, or the lack off, comparing these groups of workers.

HERBST, SARAH

Degree Sought	MD, BS, MD, BS, MD, BS, BS, MD, BS, MD
Mentor Name	PETRY, NANCY M
Period	06/01/2006 - 08/31/2006
Funds Received	3,000 *
Project Title	Lifetime mood, but not anxiety, disorders are associated with heart disease in older adults: Results from the National Epidemiologic Study on Alcohol and Related Conditions
SPIDS	0519, 0469, 0469, 0613, 0613, 0519, 0623, 0623, 0548, 0548

Project Summary

Objective: This study examined the association between mood and anxiety disorders and heart disease in a nationally representative sample of older adults. Method: Data from the National Epidemiologic Survey on Alcohol and Related Conditions (NESARC) were analyzed with 10,193 adults age sixty and older surveyed. Results: A total of 13.89% of older adults had physician-confirmed heart disease consisting of angina, arteriosclerosis, and/or myocardial infarction. Compared to those without heart disease, individuals with heart disease were more likely to be older, morbidly obese, hypertensive, and have lifetime nicotine dependence and drug use disorders. They were also less likely to be women and drink socially. After controlling for these characteristics, the presence of a lifetime mood disorder was associated with an increased risk of heart disease, but a lifetime anxiety disorder was not. Single versus multiple depressive episodes conferred equal risk of heart disease, and gender did not interact with the association between lifetime mood disorders and heart disease. Specific mood disorders that were associated with heart disease were lifetime or past-year major depression or dysthymia and lifetime manic disorder. Conclusion: These data suggest that general practitioners should consider assessing for lifetime mood disorders in their older adult patients, as even a distal experience with major depression or dysthymia may increase risk of heart disease.

LILLO, ALYSSA

Degree Sought MS, BS
 Mentor Name ISAKOFF, MICHAEL
 Period 06/01/2006 - 08/31/2006
 Funds Received 3,000 *
 Project Title Treatment of Acute Chest Syndrome in Children with Sickle Cell Disease Using Dexamethasone plus transfusion therapy: A Single Institution Experience

SPIDS

Project Summary

Acute Chest Syndrome (ACS) in children with Sickle Cell disease is one of the most common causes of morbidity and mortality in this patient population. Historically, ACS has been treated with wide spectrum antibiotics, oxygen therapy, opioid treatments, and blood transfusion. In 1998 Bernini et al published a study showing that the corticosteroid dexamethasone helped decrease the hospitalization of patients with ACS. Despite this finding, patients with dexamethasone had higher readmission rates than those not treated with the steroid. Upon empirical evidence, hematologists at Connecticut Children's Medical Center (CCMC) decided to treat children suffering with ACS through dexamethasone treatment in conjunction with blood transfusions. In order to evaluate the efficacy of CCMC's ACS treatment, we conducted a retrospective chart review of patients who had been treated according to the CCMC ACS protocol. Of the 157 charts reviewed, 63 patients were treated according to the ACS protocol. Once these patients were identified, data about their hospitalization duration, oxygen therapy duration, opioid therapy duration, readmission rate, and PICU transfer incidents were recorded. The patients were split into the two age groups 0-9 and 10-19 in order to compare the different data. Of the 63 patients evaluated, only 4 were readmitted within 72 hours. Of these 4 patients readmitted, none were readmitted for a painful crisis. Indication for a further large-scale study of this treatment is indicated by the obtained data.

SHARMA, PRIYA

Degree Sought MD, BS
 Mentor Name CLOUTIER, MICHELLE M
 Period 06/01/2006 - 08/30/2006
 Funds Received 3,000 *
 Project Title Physical Fitness of Urban Minority Children

SPIDS

Project Summary

Physical Fitness of Urban Minority Children. P.G. Sharma, BS1, D.B. Wakefield, MS1 & M.M. Cloutier, MD1,2 University of Connecticut Health Center1, Farmington, CT & Connecticut Children's Medical Center2, Hartford, CT.

Objective: The incidence of childhood obesity has doubled over the past thirty years. One in four children is at high risk for becoming obese. The growing number of obese children has been attributed to the increase in the sedentary lifestyle and to a decline in participation in physical activities. Lack of physical fitness has also been associated with increased cardiovascular risk.

Hypothesis: Children with an elevated Body Mass Index (BMI) percentile will have a decreased level of physical fitness and elevated systolic and diastolic blood pressure.

Methods: 48 urban minority children between the ages of 8-12 were recruited with parental permission from the Asylum Hill Boys and Girls Club summer program. To assess levels of physical fitness the children performed a Modified Harvard Step Test consisting of stepping up and down from a flat step (measuring 30 cm high) for a total of five minutes or as long as they could at a rate of 30 steps per minute. The duration of the test divided by the sum of the child's heart rate at 0, 1, and 2 min post exercise was used to calculate a previously validated, physical fitness score (PFS). Measurements of blood pressure, weight, height and waist to hip circumference were also taken. In addition, the children were surveyed with regard to levels of physical activity and dietary behavior.

Results: 21/48 children (43.8%) were overweight or at risk of being overweight according to BMI percentiles, while 27/48 (56.2%) children were in the normal or underweight categories. All 48 children tested had a physical fitness score greater than 65 (physically fit). BMI percentiles were negatively correlated with PFS (Pearson's correlation = -0.52, $p = 0.0002$). Although systolic blood pressure was not significantly different between the two BMI groups, systolic blood pressure was significantly correlated with elevated BMI percentiles (Pearson's correlation = 0.44, $p = 0.0019$). Partial correlations showed that systolic blood pressure was significantly correlated with BMI percentile even when controlling for PFS (Pearson Partial correlation = 0.36, $p = 0.0126$). Of the 48 children tested, 40 children (83.3%) reported playing outside daily although this did not significantly correlate with BMI percentiles or PFS. Also total time spent playing outside, time spent watching television or time spent playing video games did not significantly correlate with BMI or PFS. Dietary intake also did not correlate with BMI or PFS.

Conclusions: Children who are overweight or are at risk of being overweight demonstrated a higher systolic blood pressure than children who were normal or underweight. Being physically fit did not mitigate the cardiovascular risk defined as an increase in blood pressure that was associated with adiposity in children. This result is similar to the result found in adults.

ZABLOTSKY, ALEXANDER

Degree Sought	BS, BA
Mentor Name	PIERUCCI, AMIRA
Period	06/01/2006 - 08/31/2006
Funds Received	3,000 *
Project Title	Th Static Ataxia Response to Alcohol
SPIDS	0536, 0536
Project Summary	Using data from a study of the atypical antipsychotic drug aripiprazole, this project examined the effects of alcohol consumption on static ataxia (body sway) in normal social drinkers. Only data from the placebo conditions were utilized for this project. During the study, subjects consumed three alcoholic drinks within a 30-minute period, and were subsequently tested on subjective, cognitive, and physiological measures.

Levels of response on the body sway measure were analyzed based on gender, time, and genotype. Specifically of interest were hypothesized main effects relating to two genes thought to be related to vulnerability to alcoholism: GABRA2 and GABRG1. To date, no significant results have been obtained.

No Reported Students.

CLINICAL RESEARCH FEASIBILITY FUND (CRFF)**CONNER, TAMLIN**

Specialty Psychiatry
 Mentor Name TENNEN, HOWARD
 Funds Received 5,000

Period 05/30/2006 - 03/31/2007
 Project Title Serotonin 1A Receptor and Mood in Daily Life

Attachment(s)

Project Summary

Recent evidence identifies variation in the gene encoding the serotonin 1A (5-HT1A) receptor (genetic locus HTR1A) as a potential factor in the development of mood and anxiety disorders, with carriers of the G allele of the C(-1019)G single nucleotide polymorphism (SNP) of HTR1A being more vulnerable to such disorders than non-carriers. We request funding to examine this allelic variation and its relation to mood-related outcomes in two existing data sets- 416 DNA samples from college students taking part in an ongoing study of student life (IRB# 03-128) and 1,510 DNA samples from a larger case-control sample collected by Dr. Kranzler as part of an ongoing study of the genetics of alcohol dependence and co-morbid disorders (IRB# 96-156). The first primary aim will be to test whether variation in the HTR1A SNP predicts mood-related outcomes in the college student sample [measured by daily self-reported anxiety and other moods obtained across multiple years of study participation]and the case-control sample [measured by participants' lifetime history of DSM diagnosed major depression]. The second primary aim will be to test whether variation in HTR1A interacts with variation in the 5-HTTLPR polymorphism of the serotonin transporter gene (obtained previously in all of sample 1 and half of sample 2) to predict mood-related outcomes and lifetime history of depression. Results from primary analyses will provide pilot and feasibility data for a NIH R03 grant application by the P.I. to examine the role of serotonin-related genetic predictors of mood-related experience. A secondary aim will capitalize on existing data to determine whether variation in HTR1A and its possible interaction with 5-HTTLPR predicts differences in alcohol use for the student sample and differences in alcohol dependency in the case-control sample. Results from the secondary aim will provide pilot data for the Alcohol Research Center renewal grant to be submitted in December, 2006.

JENSEN, KEVIN

Specialty Vascular Biology
 Mentor Name FURNEAUX, HENRY M
 Funds Received 16,500

Period 05/30/2006 - 03/31/2007
 Project Title Identification of Novel 3' UTR Regulatory Variants in Candidate Genes for Substance Dependence

Attachment(s)

Project Summary

The 3' untranslated region (UTR) of mRNA is the major region of post-transcriptional gene regulation; however, the 3'UTRs of many genes for addictive disorders have not been extensively studied. Our interest is in gene regulation by microRNAs, a recently identified mechanism of post-transcriptional gene regulation. MicroRNAs anneal to the 3'UTR of mRNA and negatively regulate gene expression. An essential requirement of microRNA function is nucleotide base pairing to the 3'UTR of mRNA. **Our hypothesis is that single nucleotide polymorphisms that occur in microRNA targets will modify gene expression and contribute to addictive disorders.** Using algorithms that predict microRNA annealing to mRNA, we have successfully identified microRNA targets in the 3'UTR of the cannabinoid receptor-1 (*CNR1*) and serotonin receptor-1B (*HTR1B*) genes. These microRNA targets also contain known single nucleotide polymorphisms (SNPs) that disrupt the annealing predicted with a microRNA. Using a luciferase assay, we have shown that these SNPs release the luciferase repression conferred by the wild-type sequence. Thus these SNPs are capable of modifying gene expression. We are interested in identifying other polymorphisms that modify gene expression, and exploring their relationships with disease. However, a limitation to our current research is the lack of available 3'UTR sequence. We currently rely on SNPs deposited in the NCBI database, where there is often little information available on these polymorphisms, and many polymorphisms are yet to be discovered. Therefore **aim 1** of this proposal is to sequence the 3'UTR of the genes encoding the GABA Receptor Alpha-2 subunit (*GABRA2*), the μ -opioid Receptor (*OPRM1*), the serotonin transporter (*SLC6A4*) and *CNR1* in 100 controls, and 200 subjects with substance dependence. There is strong evidence to support the involvement of these genes in substance dependence. **Aim 2** is to explore the prevalence of the most promising polymorphism in a larger sample. The aims proposed are consistent with our current efforts to understand microRNA regulation and human disease. Specifically, data provided by this study will support an anticipated revision for a recently submitted R03, "Human Variation in microRNA Target Sites and Their Relation to Addictive Disease," and will also support a NRSA F30 submission that is planned for later this year.

KENNY, ANNE M

Specialty	Medicine
Mentor Name	FORTINSKY, RICHARD H
Funds Received	14,000
Period	05/30/2006 - 03/31/2007
Project Title	Feasibility of Multi-component Training in Patients Two Months Post Hip Fracture
Attachment(s)	

Project Summary Over 325,000 hip fractures occur in the US each year, with the cost to patients, families and the health care system estimated at between 14 and 20 billion dollars annually. (1-2) Despite improvements in medical management, significant residual disability remains in older persons post hip fracture. (3) The current practice goal for discharge from medical management at 2-3 months post surgery is independent, safe household ambulation. (4) Hip fracture-acquired dependency in functional activities of daily living persists well beyond that point: 20% of patients need help putting on pants, 50% need assistance to walk, and 90% need assistance to climb stairs 12 months after hip fracture. (5-6) These figures indicate that the current standard Medicare-reimbursed rehabilitation therapy fails to return a large proportion of patients to pre-fracture levels of function. Thus, while hip fractures are common and lead to extended disability under usual care management strategies, there is a paucity of evidence to justify extending medical management beyond the current standard in persons post-fracture.

This pilot will evaluate a 16-week, supervised multi-component intervention that is introduced as soon as the patient completes usual care (typically within two months of the fracture). The intervention has been designed to address four relevant precursors to community ambulation using stress overload and specificity of training principles. The effect of the intervention on impairments, functional limitations, and disability also will be examined.

REICHENBERGER, ERNST

Specialty	Oral Rehab, Biomaterials, & Ske
Mentor Name	SARFARAZI, MANSOOR
Funds Received	7,500
Period	05/30/2006 - 03/31/2007
Project Title	Molecular Mechanisms of Keloid Formation
Attachment(s)	

Project Summary

Keloid formation is a wound healing disorder which affects primarily darker-skinned minority populations in the US. Keloids occur sporadically or can be inherited as an autosomal dominant or recessive trait. Gene mutations and downstream cascades that are causative for keloid scarring have not been identified. Identifying such genes is fundamental to the understanding of keloid pathoetiology since biochemical and cell biological approaches have not lead to the identification of the cause for keloid formation. Keloids present an ideal model to study key mechanisms for scar formation in general.

The objective of the overall project is to identify genes and gene mutations in patients with familial keloids and to identify pathways that eventually lead to keloids. DNA samples from families where keloid formation is inherited will be collected and tested for cosegregation to several susceptibility gene loci that were already identified. Genomic DNA from families that do not map to these loci will be subjected to genome-wide screening and linkage analysis in order to identify additional keloid gene loci. Elaborate expression profiling with a large number of keloid scars using Affymetrix microarrays, and pathway profiling of positional candidate genes will 1) help to identify the best candidates for mutational analysis and 2) may identify secondary pathways which contribute to the variable expression of keloids.

The objective of the current proposal is to perform microarray genotyping using Affymetrix 10K human SNP chips with individuals from large families which have recently been collected in Nigeria. Genome screening and linkage analysis with these families are an essential part of the Preliminary Results for a competitive renewal of an expired R29 grant and will greatly increase the likelihood for funding.

THAPAR, MANISH

Specialty	Internal Medicine
Mentor Name	BONKOVSKY, HERBERT L
Funds Received	10,600
Period	08/30/2006 - 03/31/2007
Project Title	DNA Methylation Patterns in Alcoholics and Controls
Attachment(s)	
Project Summary	DNA methylation, which is thought to play an important role in carcinogenesis, is an emerging area of epigenetic research. A recent RFA (AA-06-005) from the NIH, to which a multidisciplinary investigative group from UCHC responded (Drs. Bonkovsky, Hesselbrock, Lalande, and Lambrecht) targeted epigenetic effects of alcohol and its metabolism as an important area of research. Alcohol has long been associated with cancer and has recently been associated with increased DNA methylation levels. In this pilot study, we propose to determine whether and how DNA methylation patterns in chronic alcoholics are different from suitable controls. This will be the first step in finding out if DNA methylation patterns are altered in subjects with chronic alcohol dependence and provide important pilot data for later, larger proposals to the NIH and other external funding agencies focused on mechanisms whereby alcohol and its metabolites influence cancer risk and other epigenetic effects.

WAGNER, JULIE

Specialty	Behavioral Sciences/Comm Hlth
Mentor Name	TENNEN, HOWARD
Funds Received	1,800
Period	05/30/2006 - 03/31/2007

Project Title	Daily Process Pilot Study of Discrimination Stress and Diabetes Outcomes in African American Women
Attachment(s)	
Project Summary	<p>Our group is investigating the influence of racial discrimination on diabetes outcomes among African American women. Our next step is an R01 for a daily process study that will test the hypotheses that glycemia, blood pressure, and health behaviors will be more affected by daily stress in women with high lifetime discrimination than their low discrimination counterparts. The pilot project proposed here will collect data to support that R01 application regarding the feasibility of the data collection , the acceptability of the protocol to participants, and the effect sizes among relationships. Ten diabetic AA women will wear continuous glucose sensor and ambulatory blood pressure monitoring equipment for 3 consecutive days, and report health behaviors for 7 consecutive days. Twice daily, participants will provide data on daily stressors using an interactive voice response telephone system. Information regarding recruitment, retainment, participant burden, effect sizes, technical challenges with data collection, and modification of questionnaires for daily assessment will increase the likelihood of a successful R01 application.</p>

SCIENTIFIC HIGHLIGHTS

ADDICTIONS RESEARCH

SPID(s): 0051, 0161, 0177, 0253, 0303, 0340, 0357, 0364, 0446,
0466, 0467, 0468, 0469, 0470, 0495, 0519, 0520, 0531,
0536, 0538, 0548, 0549, 0563, 0589, 0598, 0600, 0607,
0608, 0610, 0611, 0612, 0613, 0620, 0623, 0629, 0630,
0633, 0634, 0637

PAST SPID(s):

KEYWORDS: ALCOHOL, DRUGABUSE, NICOTINESMOKING

Studies in addictive behaviors, including problem drinking, dependence on alcohol, drugs and tobacco, and compulsive gambling, are major areas of National Institutes of Health (NIH) funded research carried out by University of Connecticut Health Center (UCHC) faculty. Many of these studies are conducted in the General Clinical Research Center (GCRC) and/or utilize GCRC resources, including the biostatistics, informatics, clinical, and laboratory cores.

Dr. Henry Kranzler, Professor of Psychiatry, Program Director of the GCRC, and Associate Scientific Director of the National Institute on Alcohol Abuse and Alcoholism (NIAAA) funded UCHC Alcohol Research Center (ARC) and Dr. Jonathan Covault, Associate Professor of Psychiatry, Director of the GCRC Core Laboratory and Director of the Molecular Genetics Laboratory in the Department of Psychiatry, have continued to examine candidate genes in the GABA system in relation to alcohol dependence, finding that GABGR1, the gene adjacent to GABRA2 on chromosome 4p (which has been shown in multiple studies to be associated to alcohol dependence), also shows association to that phenotype. Together with Drs. Howard Tennen, Tamlin Connor, and Henry Furneaux, and Kevin Jensen, a second-year graduate student, they have examined a microRNA mechanism regulating expression of the HTR1B gene, which encodes the serotonin 1B receptor. This group has found an association between variation in HTR1B and aggressive behaviors in a European-American (EA) college student sample. With support from the GCRC, implementation at Howard University in Washington, DC of a parallel study was successfully completed in a sample of African American students. Data from that study are currently being analyzed.

Dr. Victor Hesselbrock, Professor of Psychiatry, Chair of the GCRC Advisory Committee (GAC), Principal Investigator of the NIH-funded ARC at UCHC, and an active GCRC investigator, is a major collaborator in the multi-center Consortium on the Genetics of Alcoholism (COGA) and has also played an active role in studies of the genetics of drug dependence, which are funded as a collaborative RO1 to Dr. Kranzler at UCHC and Dr. Joel Gelernter at Yale University. Dr. Hesselbrock provides a vital connection between COGA, which continues to lead the field with respect to elucidation of the alcohol dependence phenotype and the genetic basis of the disorder, and the UCHC/Yale genetic studies of drug dependence.

Dr. Cheryl Oncken, Associate Professor of Medicine and Associate Program Director of the GCRC, continues to recruit genetics subjects for an ongoing pregnancy study that was a major component of the last GCRC competitive renewal. She is collaborating with investigators at Duke University and George Washington University to collect deoxyribonucleic acid (DNA) samples and outcome data from smoking mothers to examine genetic predictors of the fetal effects of smoking. Additional sample collection is required before meaningful analysis is undertaken.

Dr. Oncken's other projects include an examination of predictors of smoking cessation in postmenopausal women well as examining the benefits of cessation. This line of research suggests that transdermal nicotine may provide short-term benefits for smoking cessation in postmenopausal women. However, efforts are needed to improve long-term abstinence rates, and smoking outcomes among women with a history of depression. Additionally, smoking cessation increases bone mineral density at the total hip in postmenopausal women with borderline effects on the distal radius. Consequently, smoking cessation may improve health outcomes in this population. New studies initiated by Dr. Oncken and colleagues include a placebo-controlled trial of topiramate for smoking cessation.

Dr. Nancy Petry, Professor of Psychiatry, directs a highly productive and successful program studying alcohol and drug dependence and compulsive gambling. GCRC supported studies of Dr. Petry include the following, all of which continue to recruit actively: (1) An NIAAA-funded and GCRC-supported study, "Contingency management for chronic recidivist alcoholics" (2) A National Institute on Drug Abuse (NIDA) -funded study of group-based contingency management for human immunodeficiency virus (HIV) patients (3) A NIDA-funded study "Enhanced and attendance-based reinforcement in community settings" and (4) A NIDA-funded study "Prizes vs. vouchers for methadone patients." Each of these studies evaluates the efficacy of an incentive-based program to assist in retaining patients in outpatient treatment longer and enhance drug abstinence. All studies are conducted at community-based treatment programs throughout New England. This intervention has been attracting national attention with the continued dissemination of NIDA's Clinical Trials Network study utilizing this technique.

Publications:

- Zhang H, Kranzler HR, Yang B, Luo X, Gelernter G The OPRD1 and OPRK1 loci in alcohol or drug dependence: OPRD1 variation modulates substance dependence risk *Molecular Psychiatry*
- Covault J, Gelernter J, Jensen K, Anton R, Kranzler HR Markers in the 5'Region of GABRG1 associate to alcohol dependence and are in linkage disequilibrium with markers in the adjacent GABRA2 gene *Neuropsychopharmacology*
- Zuo L, Kranzler HR, Luo X, Covault J, Gelernter J CNR1 variation modulates risk for drug and alcohol dependence *Biological Psychiatry*
- Arias A, Feinn R, Covault J, Kranzler H Memantine for Alcohol Dependence: An Open-Label Pilot Study *Addictive Disorders and Their Treatment*
- Pierucci-Lagha A, Gelernter J, Chan G, Arias A, Cubells JF, Farrer L, Kranzler HR Reliability of DSM-IV diagnostic criteria using the Semi-Structured Assessment for Drug Dependence and Alcoholism (SSADDA). *Drug and Alcohol Dependence*
- Luo, X, Kranzler HR, Zuo L, Zhang H, Wang S, Gelernter J. ADH7 variation modulates Extraversion and Conscientiousness in substance dependent subjects. ADH7 variation modulates Extraversion and Conscientiousness in substance dependent subjects. *American Journal of Medical Genetics*
- Tang Y, Kranzler HR, Gelernter J, Farrer LA, Cubells JF Co-morbid psychiatric diagnoses abnd their association with cocaine-induced psychosis in cocaine-dependent subjects *American Journal on Addictions*
- Ledgerwood DM, Petry NM Does contingency management affect motivation to change substance use? *Drug Alcohol Depend* 83 65-72 2006
- Arias A, Feinn R, Kranzler HR Association of an Asn40Asp (A118G) polymorphism in the mu-opioid receptor gene with substance dependence: a meta-analysis. *Drug Alcohol Depend* 83 262-8 2006
- Zhang H, Luo X, Kranzler HR, Lappalainen J, Yang BZ, Krupitsky E, Zvartau E, Gelernter J Association between two {micro}-opioid receptor gene (OPRM1) haplotype blocks and drug or alcohol dependence. *Hum Mol Genet* 15 807-19 2006
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Foroud T, Wetherill LF, Liang T, Dick DM, Hesselbrock V, Kramer J, Nurnberger J, Schuckit M, Carr L, Porjesz B, Xuei X, Edenberg HJ Association of alcohol craving with alpha-synuclein (SNCA). Alcohol Clin Exp Res 31 537-45 2007

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Luo X, Kranzler HR, Zuo L, Zhang H, Wang S, Gelernter J CHRM2 variation predisposes to personality traits of Agreeableness and Conscientiousness. Hum Mol Genet 2007

Bone, Endocrine and Aging

SPID(s): 0410, 0413, 0433, 0448, 0461, 0523, 0542, 0557, 0588, PAST SPID(s):
0597, 0624, 0644

KEYWORDS: BONE, ENDOCRINE, AGING

Another traditional strength of the UCHC GCRC has been in the study of bone metabolism in health and disease, and productive activities in this area continue.

Drs. Pamela Taxel, Joseph Lorenzo, and Lawrence Raisz have been working to expand studies of estrogen and osteoclastogenesis that they have successfully completed using bone marrow cells to a much larger study population through the use of peripheral blood cells, which are much easier to obtain than are bone marrow cells. The laboratory techniques for culturing osteoclasts from peripheral blood mononuclear cells (PBMCs) have been developed and this group is working on studies in which they will correlate PBMC and bone marrow osteoclastogenesis with bone turnover rates in older postmenopausal women who are estrogen deficient.

In addition, several clinical trials are underway to assess the effects of hormones on bone density or bone turnover in aging adults. Dr. Anne Kenny, Associate Professor of Medicine and Associate Program Director (APD) of the GCRC, is completing a 2-year randomized trial of testosterone replacement in older men with osteoporosis and frailty, assessing the impact on bone mineral density, bone turnover, and physical performance/fall risk. She is also completing a 6-month, randomized, controlled trial of dehydroepiandrosterone and/or exercise in older postmenopausal women with osteopenia and frailty, which is also using bone turnover, physical function, and balance as outcome measures. The results from these studies will be analyzed later in 2007. Dr. Taxel is conducting clinical trials assessing the impact of alendronate and/or estrogen on bone density and markers of bone turnover in men with prostate cancer undergoing suppressive therapy with leutinizing hormone releasing hormone and women with breast cancer receiving anti-estrogen therapy.

Publications:

Boxer R, Wang Z, Hager WD, Walsh S, Kenny AM Use of the Frailty Phenotype and 6-minute Walk Test to Define a Syndrome of Pre-Frailty in Older Adults with Heart Failure American Journal of Geriatric Cardiology

Kenny AM, Waynik IY, Smith J, Fortinsky R, Kleppinger A, McGee D. Association between level of frailty and bone mineral density in community-dwelling men.J Clin Densitom. 2006 Jul-Sep;9(3):309-14. Epub 2006 May 3.

Pefanco MA, Kenny AM, Kaplan RF, Kuchel G, Walsh S, Kleppinger A, Prestwood K. The effect of 3-year treatment with 0.25 mg/day of micronized 17beta-estradiol on cognitive function in older postmenopausal women.J Am Geriatr Soc. 2007 Mar;55(3):426-31.

McNally DN, Kenny AM, Smith JA Adherence of academic geriatric practitioners to osteoporosis screening guidelines. Osteoporos Int 18 177-83 2007

Kenny AM, Boxer R, Walsh S, Hager WD, Raisz LG Femoral bone mineral density in patients with heart failure. Osteoporos Int 17 1420-7 2006

Dental

SPID(s): 0336, 0453, 0487, 0497, 0518, 0546, 0554, 0558, 0572, PAST SPID(s):
0591, 0592, 0596, 0628

KEYWORDS: DENTAL, BEHAVIOR, BONE

Investigators from the UConn School of Dental Medicine are also active in the GCRC and often collaborate with research groups in the School of Medicine. Dr. Mark Litt, Professor of Oral Health and Diagnostic Sciences, has been collaborating with Drs. Oncken and Kranzler in a study of topiramate for smoking cessation, which uses daily interactive voice response (IVR) technology to obtain multiple within-day assessments of mood and other variables

that may enhance our understanding of the mechanism of effects on risk of smoking. He also conducts research on contingency management for drinking and other substance abuses, and on short-term interventions for temporomandibular disorder (TMD). Dr. Litt's TMD study was a presented study in the GCRC's last competitive renewal.

Dr. Robert Aseltine, Associate Professor of Oral Health and Diagnostic Sciences, recently completed the data collection phase of his study on Emergency Department experiences and interventions for alcohol users. This study extensively used interactive voice response (IVR) for collecting daily information from subjects.

Dr. Julie Wagner, Assistant Professor of Oral Health and Diagnostic Sciences, demonstrated a clear dose-response relationship between depressive episodes and endothelial function measured by brachial artery flow-mediated dilation. These analyses control for a number of potential confounds, including current sub-clinical depressive episodes, ethnicity, hormone replacement therapy, and metabolic syndrome. She has also reported that among diabetic women, those with a history of fully remitted depression have higher HbA1c, more diabetes symptoms, and worse emotional functioning than their never depressed counterparts even after controlling for numerous confounds.

Dr. Rajesh V. Lalla, Assistant Professor of Oral Health and Diagnostic Sciences, received a Mentored Patient-Oriented Research Career Development Award (K23) from the National Institute of Dental and Craniofacial Research (NIDCR). As part of his K23 training, he is currently conducting two clinical research studies with GCRC support: (1) "Prevention of Recurrent Aphthous Stomatitis Using Vitamins," which will help to determine the role of vitamin deficiencies in the pathogenesis of Recurrent Aphthous Stomatitis, which is the most common ulcerative oral mucosal disease affecting humans. Conduct of this study is progressing well, with >100 subjects been enrolled to date. (2) "COX-2 Inhibition in Radiation-induced Oral Mucositis" will help elucidate the pathogenesis of this debilitating condition and may identify a new therapeutic approach. Oral Mucositis is very painful and negatively impacts nutritional intake and quality of life. Recruitment to this study has steadily improved, with a total of 15 subjects now enrolled.

Dr. Ernst Reichenberger, Assistant Professor of Oral Rehabilitation, Biomaterials and Skeletal Development, through GCRC support for a linkage study of keloid formation, was able to collect sufficient data to obtain NIH funding (R01) for an adequately powered study. That study focuses on the recruitment of families with inherited keloid formation, with a goal of identifying genetic loci and gene mutations that contribute to the disorder. Genome scans with an initial set of patients from Nigeria are currently under way. The GCRC also supported Dr. Reichenberger's projects involving patient recruitment and DNA isolation for patients and families with rare genetic disorders of the skeleton, specifically aplasia cutis congenita (ACC), craniometaphyseal dysplasia, and cherubism. This has resulted in a sufficient number of families with ACC to perform a linkage study.

Publications:

Litt, M.D., Kadden, R.M., Kabela-Cormier, E., & Petry, N.M. Changing Network Support for Drinking Initial Findings from the Network Support Project Journal of Consulting and Clinical Psychology

Aseltine R The Academic ED SBIRT Research Collaborative. An Evidence Based Alcohol SBIRT Curriculum for ED Providers Improves Skills and Utilization Substance Abuse

Wagner JA, Tennen H History of major depressive disorder and diabetes outcomes in diet- and tablet-treated post-menopausal women: a case control study. Diabet Med 24 211-6 2007

IMMUNOLOGY

SPID(s): 0292, 0325, 0439, 0486, 0496, 0524, 0566, 0585

PAST SPID(s):

KEYWORDS: IMMUNOLOGY, VACCINE,

The project by Drs. Peter Krause, Professor of Pediatrics, and Stephen Wikel, Professor of Immunology, entitled "Health Burden of Deer-Associated Zoonoses," is primarily focused on the immunologic response to deer tick bites in humans, with the long-term goal of developing a vaccine to prevent tick-borne infection in people. Current work includes a histopathologic study of dermatologic reactions to deer tick bite in mice and humans and a review of the clinical manifestations and immunopathogenesis of local and systemic reactions to deer tick bite in people. Findings to date suggest that human cutaneous hypersensitivity to tick bite alters pathogen transmission. Studies also focus on determining the underlying mechanisms of heightened resistance to tick-borne pathogen transmission and identification of tick saliva molecules responsible for inducing and eliciting protective responses. A secondary objective of the project is to investigate the health burden of human babesiosis.

Drs. Krause and Wikel recently completed a study of the pathogenesis and treatment of persistent babesiosis in immunocompromised hosts. They are also actively investigating the epidemiology of babesiosis in a highly endemic area and genetic determinants of resistance to human babesiosis and how these relate to aging.

GCRC investigators continue to pursue scientific discovery in developing vaccines. Dr. Janet McElhaney, Assistant Professor of Immunology, is working with the Centers for Disease Control and Prevention in testing influenza vaccines. Her study is now in its third year recruiting subjects, and has resulted in one publication.

Drs. Nitya Chakraborty, Assistant Professor of Hematology-Oncology, and Bijay Mukherji, Professor of Hematology-Oncology, are investigating cell behavior focused on a vaccine for prostate cancer and have received NIH funding for additional research on CTL activated cell death.

In the area of research into immunologic response, Drs. Justin Radolf, Associate Professor of Medicine, and Juan Salazar, Associate Professor of Pediatrics, continue to collaborate on a better understanding of the causes and interventions for infectious diseases such as syphilis and human immunodeficiency virus (HIV). Dr. Salazar has been principal investigator for a large number of protocols sponsored by the Pediatric AIDS Clinical Trials Group (PACTG), which recently ended. Several of those protocols were for Phase I/II HIV vaccine trials.

Publications:

Xie D, McElhaney JE Lower GrB+CD62L (high) CD8 T(CM) effector lymphocyte response to influenza virus in older adults is associated with increased CD28(null) CD8 T lymphocytes. *Mech Age Dev*. In press.

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Moore MW, Cruz AR, LaVake CJ, Marzo AL, Eggers CH, Salazar JC, Radolf JD Phagocytosis of *Borrelia burgdorferi* and *Treponema pallidum* potentiates innate immune activation and induces gamma interferon production. *Infect Immun* 75 2046-62 2007

Raju M, Salazar JC, Leopold H, Krause PJ Atovaquone and azithromycin treatment for babesiosis in an infant. *Pediatr Infect Dis J* 26 181-3 2007

Krause PJ, Foley DT, Burke GS, Christianson D, Closter L, Spielman A; Tick-Borne Disease Study Group. Reinfection and relapse in early Lyme disease. *Am J Trop Med Hyg*. 2006 Dec;75(6):1090-4.

Mehrotra S, Chhabra A, Hegde U, Chakraborty NG, Mukherji B Inhibition of c-Jun N-terminal kinase rescues influenza epitope-specific human cytolytic T lymphocytes from activation-induced cell death. *J Leukoc Biol* 81 539-47 2007

LIVER AND METABOLIC DISEASES

SPID(s): 0442, 0471, 0478, 0505, 0551, 0562

PAST SPID(s):

KEYWORDS: LIVER, METABOLISM,

Studies on diverse liver and metabolic diseases continue to be a focus of clinical and translational research in the GCRC. Dr. Herbert Bonkovsky, Professor of Medicine and former Program Director of the GCRC, is one of the principal investigators for the NIH National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) -sponsored HALT-C Trial (Hepatitis C Antiviral Long-Term Treatment to Prevent Cirrhosis). This is the major effort of the NIH to improve management and outcomes of patients with difficult to treat and cure, moderately advanced to advanced chronic hepatitis C. The study has now enrolled over 1,000 subjects into the long-term follow-up phase of the trial. Approximately one-half of the subjects are receiving long-term, low-dose pegylated interferon (Pegasys, Roche, 90 mcg/week). The other one-half of subjects are receiving no additional treatment. Both groups are being followed every three months for at least an additional 3.5 years.

Publications:

Morishima C, Morgan TR, Everhart JE, Wright EC, Shiffman ML, Everson GT, Lindsay KL, Lok AS, Bonkovsky HL, Di Bisceglie AM, Lee WM, Dienstag JL, Ghany MG, Gretch DR, HALT-C Trial Group HCV RNA detection by TMA during the hepatitis C antiviral long-term treatment against cirrhosis (Halt-C) trial. *Hepatology* 44 360-7 2006

Bonkovsky HL, Naishadham D, Lambrecht RW, Chung RT, Hoefs JC, Nash SR, Rogers TE, Banner BF, Sterling RK, Donovan JA, Fontana RJ, Di Bisceglie AM, Ghany MG, Morishima C, HALT-C Trial Group Roles of iron and HFE mutations on severity and response to therapy during retreatment of advanced chronic hepatitis C. *Gastroenterology* 131 1440-51 2006

Everson GT, Hoefs JC, Seeff LB, Bonkovsky HL, Naishadham D, Shiffman ML, Kahn JA, Lok AS, Di Bisceglie AM, Lee WM, Dienstag JL, Ghany MG, Morishima C, HALT-C Trial Group Impact of disease severity on outcome of antiviral therapy for chronic hepatitis C: Lessons from the HALT-C trial. *Hepatology* 44 1675-84 2006

Vuppalanchi R, Liangpunsakul S, Chalasani N Etiology of new-onset jaundice: how often is it caused by idiosyncratic drug-induced liver injury in the United States? *Am J Gastroenterol* 102 558-62; quiz 693 2007

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Shiffman ML, Ghany MG, Morgan TR, Wright EC, Everson GT, Lindsay KL, Lok AS, Bonkovsky HL, Di Bisceglie AM, Lee WM, Dienstag JL, Gretch DR Impact of reducing peginterferon alfa-2a and ribavirin dose during retreatment in patients with chronic hepatitis C. *Gastroenterology* 132 103-12 2007

Lok AS, Everhart JE, Chung RT, Padmanabhan L, Greenson JK, Shiffman ML, Everson GT, Lindsay KL, Bonkovsky HL, Di Bisceglie AM, Lee WM, Morgan TR, Ghany MG, Morishima C, HALT-C Trial Group Hepatic steatosis in hepatitis C: comparison of diabetic and nondiabetic patients in the hepatitis C antiviral long-term treatment against cirrhosis trial. *Clin Gastroenterol Hepatol* 5 245-54 2007

ADMINISTRATIVE NARRATIVES

ADMINISTRATION

Summary of Program Activities

The Lowell P. Weicker, Jr. General Clinical Research Center at the University of Connecticut Health Center (UConn GCRC) had a productive grant Year 13. A total of 39 new proposals were approved by the Scientific Advisory Committee, representing a variety of investigational areas. The total number of reported visits also increased substantially over year 12.

During the past grant year, the General Clinical Research Center (GCRC) supported 76 Principal Investigators and a total portfolio of 165 subprojects. Of these subprojects, 61 were performed by University of Connecticut Health Center (UHC) investigators, 6 were performed by Connecticut Children's Medical Center (CCMC) investigators, and 9 were for investigators at 8 other locations.

Key statistics for the GCRC program are summarized below:

Key Statistic	Year 10 (16 months)	Year 11	Year 12	Year 13
Subprojects	202	187	171	165
Visits -				
Outpatient visits	11,510	8,122	4,282	5,296
Scatter visits	0	5	0	63
Other res. visits	0	0	2,409	5,796
Total Visits	8,632	8,127	6,691	11,155
Publications				
Published	91	59	72	58
In press this year	7	18	14	13

Distribution of UHC based investigators by academic area is as follows: Medicine - 19, Psychiatry - 13, Dental School - 10, Surgery - 5, Immunology - 3, Genetics - 3, Occupational Medicine - 2, Pediatrics - 2, Other - 4.

The significant increase in visit volume is due to a combination of factors: the changing mix of supported subprojects including protocols with higher volumes of study visits, and a more concerted effort to capture visits supported by the GCRC but taking place outside the GCRC outpatient clinic (e.g., in other clinics and in community settings).

Personnel Changes

Several key personnel changes took place during the current grant year. In April 2006, Bruce M. Koeppen, MD, PhD, was appointed the GCRC's principal investigator, succeeding Richard Berlin, MD. Dr. Koeppen is currently Professor of Medicine and Dean for Academic Affairs for the Health Center. In August 2006 Kathleen Salomone, APRN, was hired to be the GCRC's Research Subject Advocate. Ms. Salomone, who has previously worked as a research study coordinator in the UConn GCRC, holds a joint appointment with the Human Subjects Protection Office and the Office of Research Compliance, which facilitates her interaction with the two major institutional entities charged with the protection of human subjects in research. Ms. Salomone also oversees GCRC approved studies at our consortium institution, Connecticut Children's Medical Center (CCMC).

Other staffing changes included refilling a clinical research assistant position in March 2006 and a nurse practitioner position in April 2006, and hiring a second dental assistant in July 2006.

Administrative Infrastructure Improvement

In order to better understand the GCRC program's financial condition and status of obligated funds, a software suite was selected and implemented for the grant year. It has worked well, and we expect to continue to use it for the duration of the current grant competitive cycle. The suite consists of two modules, one of which is used

to project and analyze personnel expenses for salaries and fringe benefits, and another which takes summarized information from the personnel module and then records detailed procurement transactions, including contracts. Expenses are booked and can be reported by financial account and by GCRC subproject. The software suite is reconciled to the institution's payroll and general ledger system monthly. Internal work processes have been modified to support the data entry, account reconciliation and reporting activities and staff have been trained and cross-trained on these duties.

During the grant year the GCRC program reviewed how it could support investigators in generating publications. We identified an investigator need for help in developing "mass customization" case report forms and statistical databases, and staff for data entry of case report forms into electronic datasets for statistical and scientific analyses. In the grant reporting period we requested and obtained institutional support for software licenses, hardware, and salary support to pilot the concept of a data management group, to provide data management services including data entry, for a limited number of studies. An evaluation by investigators was conducted in January 2007 and the results were encouraging. At the end of the grant reporting period the group consisted of 5 people, primary part time student laborers, led by a regular staff part time research assistant. We plan to operate this data management function for the remainder of the grant competitive cycle.

Capital Purchases

In grant year 13 the UConn GCRC increased its capabilities to support clinical research. We acquired several major capital equipment items through institutional support and through an approved carry forward of more than \$100,000 of unobligated funds from grant year 12. The total investment of over \$250,000 is summarized below.

Capital Equipment	Acquisition Cost	Funding Source
Luminex 200 Immunoassay Workstation System	\$54,356	GCRC grant
Vacuum manifold for Luminex	\$1,110	GCRC grant
Body Scan Bioelectrical Impedance Analyzer	\$4,985	GCRC grant
Revco Upright -80 Freezer	\$11,288	GCRC grant
Canon EOS 30D Digital Dental Camera	\$2,925	GCRC grant
Blickman Enclosed Metal Case Cart	\$1,811	GCRC grant
Air Techniques PeriPro X-Ray Processor	\$1,726	GCRC grant
Macan MC-4A Electro- surgery Unit	\$1,150	GCRC grant
Sorvall Legend RT tabletop refrigerated centrifuge with TTH-750 rotor	\$8,223	GCRC grant
HP replacement microtower PC workstations	\$3,024	GCRC grant
HP replacement laptop computer	\$2,124	GCRC grant

Research records moveable slide filing system	\$4,797	GCRC grant
Subtotal	\$ 97,519	
12 Channel Equalizer 384 Impact2 Electronic Pipettors	\$3,780	GCRC/ Institution
ABI 790 HT Sequence Detector Well-block	\$5,500	GCRC/ Dept of Psychiatry
Subtotal	\$ 9,280	
GE Prodigy Plus Bone Mineral Densitometer	\$78,500	Institution
HP Computer Servers for Adverse Events System	\$6,958	Institution
HP Computer Servers for Open Clinica Scientific Data System	\$18,680	Institution
Akaza Software License for OpenClinica Scientific Data System	\$19,661	Institution
Epson LCD Projector	\$4,752	Institution
HP Back-up Server for GCRC infrastructure	\$5,089	Institution
Subtotal	\$133,640	
Interactive Voice Response software licenses	\$13,032	Various GCRC principal investigators
Subtotal	\$13,032	
TOTAL	\$253,471	

The availability of these new capabilities has been communicated to the clinical research community in a variety of ways, including through institutional broadcast messages, the GCRC seminar series, the GCRC newsletter, and our website. It is hoped that the expanded functionality will increase future clinical research productivity.

BIostatistician

The Biostatistics Core (BC) works with established and potential GCRC investigators in the development and design of new research projects. It also performs analysis of data from GCRC protocols and guides GCRC investigators and staff members in conducting their own data analyses. The designated GCRC Biostatistician, Dr. Stephen Walsh, also reviews the study design and power as well as planned analytical methods for all new proposals presented to the GCRC Advisory Committee. BC staff also participate in the GCRC Principles of Clinical Research course by presenting lectures concerning basic statistical theory, study design, data analysis, and use of statistical software.

Staffing

Throughout all but the last month of funding for Year 13, BC staff included two doctoral-level faculty members and a master's-level statistician. The BC was directed by Dr. Stephen Walsh. Dr. Walsh provided consultations to GCRC investigators and also served as a member of the Executive Committee and of the GAC. His role on the GAC was to review the statistical integrity of every new protocol submitted to the GCRC. In addition, he taught in both semesters of the Principles of Clinical Research course, providing a total of 12 hours of lectures. Dr. Walsh's salary support was provided by the Dean of the School of Medicine using state funds; he received no salary support from the GCRC award for Year 13.

The Center's other faculty member, Dr. John Tsimikas, received salary support from the GCRC at the 50% -level of effort. He provided statistical consultations to GCRC investigators, offered 12 hours of lectures within the Principles of Clinical Research Course, and worked one-on-one with the course participants in completing their research projects. Dr. Tsimikas ended his employment at UConn in March, 2007, - i.e., the last month of Year 13 funding. Current plans are for Dr. Walsh to assume his responsibilities within the GCRC during Year 14 of funding.

The Center's master's-level statistician, Ms. Deborah Dauser-Forrest, received 25% salary support from the GCRC throughout the past year and conducted data analysis for GCRC projects under the direction of Drs. Walsh and Tsimikas. She also monitored subject recruitment to GCRC protocols and documented each protocol's progress in achieving recruitment objectives.

CORE LAB

Volume of Services

During the April 2006 - March 2007 year 13 grant period, the Core Laboratory reported 30,416 assay results including 6,490 hormone or protein analyte results, 20,281 genotype results, 555 DNA sequence analysis of PCR amplicons, isolated DNA or RNA from 3,021 samples, and analyzed 69 blood samples by FACS. This represents an average annual increase of 4.8% in the number of assays over the past 3 years. The core lab additionally prepared some 14,000 aliquots for storage or shipment from 8,900 patient samples.

New Capabilities

During this past year we have purchased and installed a commercial software package, FreezerWorks for sample storage and tracking. Clinical research samples are logged into the system in the clinical unit by the Core Lab sample processing staff and subsequent aliquot storage or transfer of samples is managed using the software. This represented a significant time investment by the lab staff initially but will provide improved efficiencies and accuracy in locating samples for assay going forward. We also purchased a Luminex based multiplex immunoassay system to allow reduced reagent costs, reduced staff time and the capacity to perform multiple assays on limited sample volumes.

CLIA Certification

The Core Laboratory continues to be licensed by the State of Connecticut Department of Public Health with a CLIA certification, with our most recent 2-year inspection in August 2006, no deficiencies were identified.

INFORMATICS CORE

The Informatics Core continues to manage and develop a variety of platforms and functions that are key to the research and administrative functions of the GCRC.

Interactive Voice Response

The Interactive Voice Response System (IVRS), which was acquired in the Fall of 2002, continues to grow rapidly. The system, which is used to host and administer phone-based interviews, now, has 90 telephone lines, supporting 21 funded studies. Five of the studies belong to investigators at other institutions, which include Yale University (Dr. Tami Sullivan), University of Michigan (Dr. James Cranford), the University of Chicago (Dr. Andrea King), the University of Connecticut-Storrs (Dr. William Barta), and the Institute for Community Research in Hartford, CT (Dr. Jean Schensul). The table below provides information on active and completed IVR studies and the following table provides information on pending and proposed studies.

In the past year, the system administered over 65,000 calls to 800 study participants, and lasting approximately 2,000 hours. This effort has thereby substantially reduced staff time required to collect data from participants and has eliminated the time required for double entry of these data (increasing the accuracy of the data as well). The IVR System represents one of the great successes of the Informatics Core, but as such has required substantial time and effort from Dr. Abu-Hasaballah, our Informatics Core Director, and his staff.

OpenClinica

We deployed OpenClinica, a web-based, HIPAA-compliant, centralized database application to manage the scientific data for all of our research protocols, early this year. Our goal in the early months of operating this system was to stress-test it to expose any weaknesses that would prevent us from making a long-term commitment. The tests revealed a number of flaws and weaknesses that prevented us from committing to the system until they are resolved by the vendor. Some of the flaws were, a hard to navigate user system interface, inherent risky underlying data structure, and an overall system that was not mature enough. As an alternative, we've adopted SPSS Data Entry/Builder for case report form (CRF) design and data entry.

Integrated Information System

Our Integrated Information System (IIS), a web-based application developed in-house for electronic submission and management of GCRC resource utilization, staff task reporting, and study participant visit tracking, is in its second year of production. A number of reports and features were added to the system to enhance data quality and increase its utility in the operation of the GCRC.

Scientific Accomplishments

Dr. Khamis Abu-Hasaballah, Informatics Director, delivered a number of lectures on Medical Informatics, HIPAA rules and institutional standard operating procedures regarding email communications between doctors and their patients, and clinical research and data security. Also, he is a lead author on a manuscript entitled "Lessons and pitfalls of interactive voice response in medical research," published in *Contemporary Clinical Trials* in 2007 (PMID: 1740052).

Ongoing and Completed IVR Studies

GCRC SPID #0487

Title: Cyclooxygenase-2 Inhibition in Radiation-Induced Oral Mucositis

PI: Rajesh Lalla, BDS, PhD

Institution: UConn Health Center

Study Area: Cancer, Daily monitoring

Funding Agency: Partially By Pfizer

Study Status: Active

Total Research Subjects: 7

Total IVR Calls: 156

GCRC SPID #0495

Title: Targeted Naltrexone for Problem Drinkers

PI: Henry R Kranzler, MD
Institution: UConn Health Center
Study Area: Alcohol, Daily assessment
Funding Agency: NIAAA
Study Status: Active
Total Research Subjects: 166
Total IVR Calls: 10,979

GCRC SPID #0497
Title: Brief Focused Treatment for TMD: Mechanisms of Action
PI: Mark Litt, PhD
Institution: UConn Health Center
Study Area: Symptom monitoring, Momentary assessment
Funding Agency: NIDCR
Study Status: Active
Total Research Subjects: 93
Total IVR Calls: 4,273

GCRC SPID #0531
Title: Sertraline Pharmacotherapy for Alcoholism Subtypes
PI: Henry R Kranzler, MD
Institution: UConn Health Center
Study Area: Alcohol, Daily assessment
Funding Agency: NIAAA
Study Status: Active
Total Research Subjects: 96
Total IVR Calls: 5,690

GCRC SPID #0538
Title: Combination Nicotine Replacement for Alcoholic Smokers
PI: Mark Litt, PhD
Institution: UConn Health Center
Study Area: Alcohol, Smoking, Momentary assessment
Funding Agency: NIAAA
Study Status: Completed
Total Research Subjects: 118
Total IVR Calls: 12,946

GCRC SPID #0554
Title: Emergency Department Alcohol Screening Project (14-site study; UCHC is coordinating center)
PI: Robert H. Aseltine, PhD
Institution: UConn Health Center
Study Area: Alcohol
Funding Agency: NIAAA
Study Status: Completed
Total Research Subjects: 1,734
Total IVR Calls: 1,837

GCRC SPID #0559
Title: Assess the Feasibility of a Daily Process Study of HIV Risk Behavior Among HIV Positive Individuals Living in Poverty
PI: William Barta, PhD
Institution: UConn, Storrs
Study Area: HIV, Daily assessment
Funding Agency: Pilot
Study Status: Completed
Total Research Subjects: 18
Total IVR Calls: 292

GCRC SPID #0563

Title: Alcohol Stimulation and Sedation in Binge Drinkers
PI: Andrea King, PhD
Institution: University of Chicago
Study Area: Alcohol
Funding Agency: NIAAA
Study Status: Active
Total Research Subjects: 186
Total IVR Calls: 696

GCRC SPID #0569
Title: Breaking the Cycle of Behavioral Health Problems
PI: Julian Ford, PhD
Institution: UConn Health Center
Study Area: Domestic Violence, Daily assessment
Funding Agency: NIH
Study Status: Active
Total Research Subjects: 190
Total IVR Calls: 4,710

GCRC SPID #0573
Title: Maintenance of Treatment Gains in Adolescents with Alcohol Related Disorders: Measurement of Daily Alcohol and Drug use by Phone using IVR (Pilot)
PI: Yifrah Kaminer, MD
Institution: UConn Health Center
Study Area: Alcohol, Daily assessment
Funding Agency: NIAAA
Study Status: Completed
Total Research Subjects: 27
Total IVR Calls: 269

GCRC SPID #0589
Title: Individualized Assessment and Treatment for Alcohol
PI: Mark Litt, PhD
Institution: UConn Health Center
Study Area: Symptom monitoring, Momentary assessment
Funding Agency: NIH
Study Status: Active
Total Research Subjects: 65
Total IVR Calls: 5,175

GCRC SPID #0592
Title: Prevention of Recurrent Aphthous Stomatitis Using Vitamins
PI: Raj Lalla, BDS, PhD
Institution: UConn Health Center
Study Area: Medication Adherence and Symptom
Funding Agency: Donaghue Foundation
Study Status: Active
Total Research Subjects: 96
Total IVR Calls: 2,467

GCRC SPID #0605
Title: HIV Risk Behavior Among HIV Positive Individuals Living in Poverty
PI: William Barta, PhD
Institution: UConn, Storrs
Study Area: HIV, Daily assessment
Funding Agency: NIAAA
Study Status: Completed
Total Research Subjects: 203
Total IVR Calls: 5,256

GCRC SPID #0611

Title: Topiramate Alone and in Combination with the Nicotine Patch for Smoking Cessation: A Pilot Study

PI: Cheryl Oncken, MD

Institution: UConn Health Center

Study Area: Smoking, Symptom monitoring, Momentary assessment

Funding Agency: Not Funded - Pilot

Study Status: Active

Total Research Subjects: 44

Total IVR Calls: 1,933

GCRC SPID #0618

Title: Girls in Recovery from Life Stress

PI: Julian Ford, PhD

Institution: UConn Health Center

Study Area: Stress, Daily assessment

Funding Agency: Dept. of Justice

Study Status: Active

Total Research Subjects: 31

Total IVR Calls: 238

GCRC SPID #0627

Title: Place-based Social Marketing to Prevent Urban Youth Party Drug Use

PI: Jean Schensul

Institution: Institute for Community Research

Study Area: Drug, Alcohol

Funding Agency: CDC

Study Status: Terminated

Total Research Subjects: 0

Total IVR Calls: 0

GCRC SPID #0622

Title: The Temporal Relationship of Partner Violence

PI: Tami Sullivan, PhD

Institution: Yale University

Study Area: Domestic Violence, Daily monitoring

Funding Agency: NIH

Study Status: Active

Total Research Subjects: 0

Total IVR Calls: 0

GCRC SPID #0636

Title: Evaluating Sensitivity to Within-Person Change

PI: James Cranford, PhD

Institution: University of Michigan

Study Area: Mood, Alcohol, Daily monitoring

Funding Agency: NIH

Study Status: Active

Total Research Subjects: 20

Total IVR Calls: 156

GCRC SPID #0628

Title: Racism Daily Process

PI: Julie Wagner, PhD

Institution: UConn Health Center

Study Area: Daily monitoring

Funding Agency: State of CT

Study Status: Active

Total Research Subjects: 6

Total IVR Calls: 68

GCRC SPID #0364

Title: Marijuana Treatment Program

PI: Ronald Kadden, MD

Institution: UConn Health Center

Study Area: Daily monitoring

Funding Agency: NIH

Study Status: Active

Total Research Subjects: 9

Total IVR Calls: 180

Pending and Proposed IVR Studies

Title: Efficacy of Naltrexone in Women Smoking Cessation (C-SToP)

PI: Andrea King, PhD

Institution: University of Chicago

Study Area: Alcohol, Smoking, Naltrexone, Medication Adherence

Funding Agency: NIH

Study Status: Pending

Title: Cannabis Use, Decision-Making, & HIV Risk Among Disadvantaged Emerging Adults

PI: William Barta, PhD

Institution: UConn, Storrs

Study Area: Daily monitoring

Funding Agency: N/A

Study Status: Proposed

Title: Novel Methods to Study Substance Use in College Students

PI: Jonathan Covault, M.D., Ph.D.

Institution: UConn/Howard University

Study Area: Daily monitoring

Funding Agency: N/A

Study Status: Proposed

Title: Evaluating Changes to the Local Food Environment

PI: Ann Ferris, PhD

Institution: UConn, Storrs

Study Area: Daily monitoring

Funding Agency: N/A

Study Status: Proposed

Title: Treatment of Adolescent Alcohol Use Disorders

PI: Yifrah Kaminer, MD

Institution: UConn Health Center

Study Area: Daily monitoring

Funding Agency: N/A

Study Status: Proposed

Title: Concurrent Alcohol and Smoking Treatment: Effect on Alcohol Relapse Risk

PI: Ned Cooney, MD

Institution: UConn/Yale University

Study Area: Daily monitoring

Funding Agency: N/A

Study Status: Proposed

Title: Exercise and Smoking

PI: Cheryl Oncken, MD

Institution: UConn/University of Minnesota

Study Area: Daily monitoring

Funding Agency: N/A

Study Status: Proposed

Title: Price Elasticity for Heroin Users
PI: Todd Olmstead, MD
Institution: UConn Health Center
Study Area: Daily monitoring
Funding Agency: N/A
Study Status: Proposed

NURSING

Staffing and Clinical Capabilities

The Clinical Core continues to use a combination of clinical research nurses and clinical research assistants (CRA) to meet current and anticipated research study needs. Currently, the clinical core consists of the following professional staff: 1 APRN who serves as both a nurse practitioner and a research facilitator, 4 RNs who serve as research facilitators (RF), (3 full-time, one part-time) 1 clinical research nurse (CRN), 2 clinical research assistants (CRA), and 2 part time dental assistants (DA), each of whom coordinates 4-18 clinical research protocols. Many of the staff members are certified by the Society of Clinical Research Associate (SoCRA); 3 of the newer GCRC clinical core members sat for the June 22, 2007 certification exam for which the results are pending.

In the last year changes in the Clinical Core have included the medical credentialing of the GCRC APRN through the University's Medical Staffing Services Office. This has increased GCRC services available to investigators, particularly those who require midlevel provider support services such as histories & physicals, and certain study-specific procedures. The second change has been in the area of staff professional development. Regrettably, the GCRC lost a veteran CRA who recently graduated from nursing school and has transferred to the UCHC hospital where she will be working as an acute care nurse. Her expertise, particularly in the area of subject interactions and regulatory services, will be difficult to replace and will be sorely missed.

Lastly, and on a more positive note, one of our CRNs was reclassified to the more senior position of RF and one of our CRA 1 was reclassified to a CRA 2, both well-deserved reclassifications.

Thomas Kiely, RNC, Nurse Manager continues to review currently active GCRC clinical studies to identify the staff expertise needed. Over the last year the clinical research teams, consisting of a RF and a CRA, have proved to be a valuable combination that can share the coordinating efforts for several protocols. In these situations, the RF (a registered nurse) serves as the team leader. This approach has three strengths: it provides for staff cross-coverage, it helps to ensure that all aspects of a study are adequately addressed, and it allows staff to complement one another in terms of their skills, so that each team has the complement of clinical core skills necessary to complete all phases of a clinical study.

Research Coordinator Training

The GCRC Clinical Core will, for the sixth year, provide a 2-day Clinical Research Coordinators Course. The course will be offered next on October 3-4, 2007. It provides participants with Connecticut Nurses' Association continuing education units (CEU), which are approved by the American Nurses Credentialing Center's Commission on Accreditation. The course serves to introduce the principles of clinical research to CRAs, technicians, nurses, and others interested in study coordination. Didactic information and resource identification by experienced research personnel are provided over the 2-day period.

The goal of the course is to promote a conceptual awareness that distinguishes research practice from clinical practice. The participants attend sessions led by staff from the GCRC, Clinical Trials Unit, Human Subjects Protections Office, and Department of Pharmacy. The 16-hour course reviews the research process, with an emphasis on the many facets of coordination that are necessary for safe and effective clinical research. Topics covered include subject recruitment, compliance, IRB review, industry-sponsored studies, the drug development process, adverse event reporting, informatics, and fiscal compliance. Participant evaluations indicate that the course, which draws students from throughout the Greater Hartford region, is very highly valued.

OTHER**DENTAL**

Dental clinic activity increased again this year by 31% with 714 patient visits accommodated in the Dental Clinical Research Center (DCRC). An additional 200 dental research patient visits occurred in medical spaces of the GCRC and at Hartford Hospital. With the clinic open approximately 6 half-days per week, this translates into about 2.5 research patient visits per open session. Dental faculty were engaged in 11 active studies (approximately \$2.6 million in direct costs during this fiscal year) most of which will continue into fiscal year '07- '08. In the upcoming year the DCRC will accommodate at least one new R01 and a GCRC-funded pilot project.

Early in the year the DCRC hired a 0.6 FTE dental assistant and began mentoring her in study coordination and research patient contact functions.

Plans are being developed by the institution to reconfigure clinical dental space. It is anticipated that these plans will necessitate relocation of the DCRC. The NCRP will be provided with details related to this relocation, when such plans are finalized. A request for approval of the relocation will be made at that time.

EDUCATION AND TRAINING

This was an important year for our activities in education and training. Under the leadership of Dr. Anne Kenny, a plan for a Master of Science in Clinical and Translational Research (MSCTR) was developed. The proposal has been through a number of key University committees and now is scheduled to go to the State Board of Higher Education for review. Beginning in September of 2007 this will be our major formal didactic offering in clinical research.

The GCRC course "Principles of Clinical Research" was quite successful during the past year under the leadership of Dr. Howard Tennen. A smaller group of students was admitted (15 in the first semester and 4 in the second semester) allowing for substantially greater exchange and individual teaching. The new MSCTR degree program will have a more extended, three semester introductory course. For those who are not in the program we are currently planning for a didactic "Principles of Clinical Research" offering which will consist of a combination of video lectures with only a few face to face meetings with the students. This presumably will be a one semester course and might be given more than once a year.

This was a banner year for GCRC-sponsored seminars. From July, 2006 through June, 2007, a total of 32 seminars were held (the largest number ever offered in a year by the GCRC), with an average attendance of 35 people at each seminar.

We had six summer clinical research scholars sponsored by the GCRC in the summer of 2006, two college students and four medical students. The summer scholar seminars on clinical research, which ran for eight weeks, were open to all summer students at the Health Center and were attended by 9-14 students each week.

PROGRAM DIRECTION

Principal Investigator

Dr. Bruce Koeppen, Principal Investigator for the UCHC GCRC, continues to meet monthly with the GCRC Executive Committee. These meetings provide a forum to plan for the GCRC and to coordinate GCRC activities with other research activities at UCHC. A major current topic of discussion at the Executive Committee is the proposed relocation of some GCRC activities to a location outside the hospital building at UCHC. The rationale for this move is to provide a centralized location for the institution's clinical research activities.

Program Director

Henry Kranzler, M.D., Professor of Psychiatry, continues in the role of Program Director. Dr. Kranzler is an NIH-funded clinical investigator with a research program that focuses on the pharmacological treatment of alcohol dependence (one of the top 10 priority goals of the NIH) and on the genetics and pharmacogenetics of alcohol and drug dependence. In the past year, Dr. Kranzler stepped down from his role as Associate Dean for Clinical and Translational Research; Dr. Koeppen is now leading the planning effort for an application for a Clinical and Translational Research Award.

Other Leadership

The leadership of the GCRC continues to include three Associate Program Directors. Anne Kenny, M.D., Associate Professor of Medicine, and Cheryl Oncken, M.D., Associate Professor of Medicine, and Lawrence Raisz, M.D., Professor of Medicine, share this role. This arrangement has served the GCRC very well, and we expect to continue it for the foreseeable future. Institutional support is provided to augment MO1 support for these individuals, so that the total support for the Associate Program Directors from the GCRC grant continues to be 0.25 FTE.

Lesley Mancini, M.B.A. continues to serve as the Administrative Director and Thomas Kiely, R.N. is the Nurse Manager and Director of the Clinical Services Core. The directors of the other cores continue as before: Jonathan Covault, Ph.D., M.D. continues as Director of the Core Laboratory; Khamis Abu-Hasaballah, Ph.D. continues as Director of the Informatics Core; J. Robert Kelly, D.D.S., Sc.D. continues as Director of the Dental Clinical Research Core; and Stephen Walsh, Sc.D. continues as Director of the Biostatistics Core.

Research Subject Advocate

Kathleen Salomone, A.P.R.N., M.S., has assumed the role of Research Subject Advocate (RSA), a 70% position. Ms. Salomone's position includes 30% time with the UCHC Human Subjects Protection Office (which oversees the function of the UCHC Institutional Review Boards), supported by institutional funds. Ms. Theresa George assists Ms. Salomone in discharging the duties of the RSA.

RES SUBJECT ADVOCACY

Our Research Subject Advocate (RSA) position was filled in September 2006 with the hiring of Kathy Salomone, MSW, APRN. Ms. Salomone reports to the Principal Investigator of the GCRC Grant, Dr. Bruce Koeppe and works closely with the GCRC Program Director, Dr. Henry Kranzler, GCRC staff and investigators and the Human Subjects Protection Office of the University. Ms. Salomone comes to this position with 19 years of outpatient pediatric clinical experience and 5 years as a research facilitator.

The RSA ensures that every protocol reviewed by SAC at the SAC monthly meeting has a Data Safety Monitoring Plan/ Board commensurate with the protocol risk. She reviews protocols and informed consents submitted to SAC both at the time of initial review and continuation. At the time of continuation, she also reviews each GCRC supported study for protocol deviations, proper filing of adverse events, and effective monitoring of the study. She also participates in Project Review Team, Scientific Advisory Committee, Project Initiation Meetings and Executive Committee.

Ms. Salomone works closely with new investigators assisting them with the IRB application process and helping them develop Data and Safety Monitoring Plans appropriate to their protocol.

She also collaborates with the Human Subjects Protection Office in providing appropriate monitoring of GCRC supported studies. Her goal is to randomly monitor at least 10% of the GCRC supported protocols over the course of a year.

Ms. Salomone also works closely with research staff at the Connecticut Children's Medical Center, a UCHC Collaborating Institution. She has assisted investigators at CCMC with properly invoking the Collaborative Agreement between the two institutions. She presented to the CCMC Research Compliance Committee regarding the role of the RSA and Data and Safety Monitoring Plans.

Finally, Ms. Salomone serves on the Research Adverse Events Committee, a sub-committee of the Human Subjects Protection Office. This committee is charged with the responsibility of reviewing research-related Serious Adverse Events with the mission of protection of research subjects. She is one of three primary reviewers of serious adverse events (SAEs) submitted via on the UCHC on-line reporting system.

RESEARCH BIONUTRITION

Not Applicable

COMMITTEE MEMBER INFORMATION

*Voting

Committee Member
Area of Expertise
Department

Committee Member
Area of Expertise
Department

ADVISORY COMMITTEE (Internal)

*HESSELBROCK, VICTOR M PHD

Psychiatry
 PSYCHIATRY

*RAJAN, THIRUCHANDURAI V MD, PHD

Immunology
 Pathology

ABU-HASABALLAH, KHAMIS (Non-Voting) PHD

Informatics Director, GCRC
 Psychiatry

BAUER, LANCE D PHD

Psychiatry
 PSYCHIATRY

BURKE, GEORGINE (Non-Voting) PHD

Research Administration, CCMC
 PEDIATRICS
 CONNECTICUT CHILDREN'S MEDICAL CT USA

BURKI, NAUSHERWAN K MD

Medicine
 Medicine/Pulmonary Medicin

COVAULT, JONATHAN (Non-Voting) MD, PHD

Psychiatry
 Psychiatry

FIFIELD, JUDITH PHD

Family Medicine
 Family Medicine

FURNEAUX, HENRY M PHD

Center for Vascular Biology
 VASCULAR BIOLOGY

GRAVELEY, BRENTON R PHD

GENETICS AND DEVELOPMENTAL BIOLOGY
 GENETICS AND DEVELOPMENTAL

HAGADORN, JAMES MD

Neonatology, CCMC
 NEONATOLOGY
 CONNECTICUT CHILDREN'S MEDICAL CENTER CT USA

KELLY, JOHN R (Non-Voting) DDS, DSC

Dental
 Oral Rehab, Biomaterials

KENNY, ANNE M (Non-Voting) MD

Medicine, Geriatrics
 CENTER ON AGING

KIELY, THOMAS (Non-Voting) BSN

Clinical Core Manager, GCRC
 GCRC

KOEPPEN, BRUCE (Non-Voting) MD, PHD

Medicine
 Medicine

KRANZLER, HENRY R (Non-Voting) MD

Psychiatry
 PSYCHIATRY

LALLA, RAJESH V BDS, PHD

Oral Health and Diagnostic Sciences
 ORAL DIAGNOSIS

MANCINI, LESLEY (Non-Voting) MBA

ADMINISTRATIVE DIRECTOR, GCRC
 GCRC

ONCKEN, CHERYL (Non-Voting) MD

Medicine
 Medicine

PILBEAM, CAROL C MD, PHD

Medicine
 MEDICINE

RAISZ, LAWRENCE G (Non-Voting) MD

Medicine
 Medicine/Endocrinology

SALOMONE, KATHLEEN (Non-Voting) RN

Research Subject Advocate
 GCRC

TANNENBAUM, SUSAN MD

Hematology-Oncology
 Medicine/Hem-Onc

WAGNER, JULIE PHD

Behavioral Health/Psychiatry
 Behavioral Sci & Comm Hlth

WALSH, STEPHEN J SCD

Biostatistics
 Ctr for Biostatistics

WOLFSON, LESLIE MD

Neurology
 Medicine/Neurology

EQUIPMENT PURCHASES

Luminex 200 Immunoassay workstation

COST: \$54,356.00

This workstation allows multiplex assay of analytes from a panel of available immunoassays including most cytokines and cardiac markers. The technology utilizes fluorescence color-coded antibody coated beads and microfluidic analysis equipment to allow assay of multiple analytes on a single small sample volume.

This platform will yield supplies cost savings. With the current ELISA method assays would cost \$41,000 in supplies. The same assays with the Luminex would be \$13,800.

In addition to reducing supply cost, there is a savings in staff time as multiple analytes are examined in a single assay.

Finally, smaller sample volume would allow support for studies from pediatric subjects, CSF or other sources in which sample volume is limiting.

Revco upright -80 freezer

COST: \$11,288.00

This additional -80 freezer for the Core Lab will be used to store temporary tissue/sample collections that occur at non-GCRC performance sites.

Current needs are for support of GCRC protocols involving the collection of umbilical cord, cord blood and placenta samples in the labor and delivery area at affiliated hospitals and for plasma/serum samples collected at the University of Connecticut Storrs campus.

Although the GCRC currently operates 6 freezers, they are at capacity and there is insufficient storage room.

Brachial Artery Analyzer software

COST: \$8,995.00

The software consists of four modules: brachial analyzer, doppler flow analyzer, vascular HP sonos converter and vascular dicom module. It provides methods for looking at ultrasound images and assigning standardized quantitative metrics to describe the images, compare them to other images and calculate variations for a research subject or across a subset of subjects.

The software makes interpreting brachial artery ultrasounds less subjective and requires less investigator experience for successful analyses.

The software is currently used to support 3 GCRC cardiology studies.

Sorvall Refrigerated Centrifuge

COST: \$8,223.00

This centrifuge will be used to prepare ABI 7900 HT system microfluidic PCR assay plates used in low-density array RT-PCR assays of mRNA levels. Such assays are requested by investigators for quantitative assay of gene expression as a function of disease state, environmental exposure, or drug treatment.

Previously, the GCRC had to borrow a centrifuge from the Dept of Psychiatry and a rotor from the Dept of Genetics and Developmental Biology to enable preparation of low density 384-well RT-PCR assay microfluidic cards for PCR thermocycling in the ABI 7900HT instrument.

The new centrifuge is also used for standard sample processing in the Core Lab, allowing use of a current non-refrigerated instrument for sample processing at off-site blood collections.

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