

2008

# Annual Report General Clinical Research Center 2007/2008

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**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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**5M01RR006192-14**

**GENERAL CLINICAL RESEARCH CENTER**

Final

**UNIVERSITY OF CONNECTICUT HEALTH CENTER**

SCHOOL OF MEDICINE

**ANNUAL PROGRESS REPORT**

Reporting From: 04/01/2007

Reporting To: 03/31/2008

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Signature

Date

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**PERSONNEL ROSTER**

\*Current CAP, -Previous CAP, + Minority

<b>Name, Degree</b>	<b>Department</b>	<b>Non-Host Institution: State, Country</b>
ABU-HASABALLAH, KHAMIS, PHD	Psychiatry	
ADAMS, NANCY, MD	Medicine/Nephrology	
AFFLECK, GLENN, PHD	Community Medicine	
ALBERT, DAVID, PHD	Psychiatry	
ALBERTSEN, PETER, MD	Surgery	
ALESSI, SHEILA, PHD	Psychiatry	
ALLEN, HOLLY, MD	PEDIATRIC ENDOCRINOLOGY	BAYSTATE MEDICAL CENTER: MA, USA
ARIAS, ALBERT, MD	Psychiatry	
ARMELI, STEPHEN, PHD		PACE UNIVERSITY: NY, USA
ARNOLD, ANDREW, MD	Medicine	
ASTUR, ROBERT, PHD	OLIN CENTER	HARTFORD HOSPITAL: CT, USA
AZIZ, KHALID, MD	Medicine	
BABOR, THOMAS, PHD	Community Medicine	
BAUER, LANCE, PHD	Psychiatry	
BENMAMOUN, CHOUKRI, MD	Microbial Pathology	
BONA, ROBERT, MD	Medicine/Hem-Onc	
BONKOVSKY, HERBERT, MD	Medicine/Gastroenterology	
BOXER, REBECCA, MD	Medicine/Geriatrics	
BRUNO, RICHARD, PHD, RD	NUTRITIONAL SCIENCES	UCONN STORRS: CT, USA
BURKI, NAUSHERWAN K, MD	Medicine/Pulmonary Medicin	
BURLESON, JOSEPH, PHD	Behavioral Sciences	
CABRAL, CYNTHIA, BS	Dental-Students	
CALHOUN, VINCE, MD	PSYCHIATRY	YALE UNIVERSITY: CT, USA
CAMPBELL, WINSTON, MD	Obstetrics/Gynecology	
CAPRIGLIONE, ANTOINETTE, MD	OB/GYN	NEW BRITAIN GENERAL HOSPITAL: CT, USA
CARROLL, CHRISTOPHER, MD	PEDIATRICS	CONNECTICUT CHILDREN'S MEDICAL: CT, USA
CARROLL, KATHLEEN, PHD	PSYCHIATRY	YALE UNIVERSITY: CT, USA
CHAKRABORTY, NITYA G, PHD	Medicine	
CHERNIACK, MARTIN, MD	Occupational/Environmental	
CILLESSEN, ANTONIUS, PHD	PSYCHOLOGY	UCONN, STORRS: CT, USA
CLARK, ROBERT, MD	Immunology	
CLOUTIER, MICHELLE, MD	Pediatrics	
COBB, RICHARD, MD	Diagnostic Imaging	
CONNER, TAMLIN, PHD	Psychiatry	
CONWAY, JUDITH, ARNP	CANCER CENTER	
COONEY, JUDITH, PHD	PSYCHIATRY	YALE UNIVERSITY: CT, USA
COONEY, NED, PHD	PSYCHIATRY	YALE UNIVERSITY: CT, USA
COVAULT, JONATHAN, MD, PHD	Psychiatry	
CRANFORD, JAMES, PHD	SUBSTANCE ABUSE RESEARCH	UNIVERSITY OF MICHIGAN: MI, USA
DAMATO, KATHRYN L, MS	Oral Diagnosis	
DANNENBERG, ANDREW J, MD	GASTROENTEROLOGY/HEPATOLOG	CORNELL UNIVERSITY: NY, USA
DAVENPORT, MARSHA, MD	PEDIATRICS	UNIVERSITY OF NORTH CAROLINA: NC, USA
DECKERS, PETER, MD	Surgery	
DEHART, TRACY, PHD	PSYCHOLOGY	LOYOLA: IL, USA
DEMARTINIS, NICHOLAS, MD	Psychiatry	
DIECKHAUS, KEVIN, MD	Medicine/Infectious Diseas	
DIPASQUALE, CHRIS, PHD	KINESIOLOGY	UCONN - STORRS: CT, USA
DONGARI-BAGTZOGLU, ANNA, DDS, PHD	Periodontology	
DORSKY, DAVID, MD	Infectious Disease	

DOUGLAS, KARA R, BS	GCRC	
DOWSETT, ROBERT J, MD	Radiation Oncology	
DRAZINIC, CAROLYN, MD	Psychiatry	
DUCK, KIM, PHD	Surgery	
DUFFY, VALERIE, PHD	ALLIED HEALTH SCIENCES	UCONN, STORRS: CT, USA
ELSHEICKA, HANY, MD	Center for Microbial Patho	
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	
FEINN, RICHARD, PHD	Psychiatry	
FISHER, JEFFREY D, PHD	PSYCHOLOGY	UCONN - STORRS: CT, USA
FORD, JULIAN, PHD	Psychiatry	
FORMAKER, BRADLEY, PHD	Oral Health & Diagnostics	
FORTINSKY, RICHARD, BA	Center on Aging	
FRANK, MARION, DMD	Oral Diagnosis	
FREILICH, MARTIN A, DDS	Prosthodontics	
FRESTON, JAMES, MD	Medicine	
FRIEDLAND, GERALD, MD	PSYCHIATRY	YALE UNIVERSITY: CT, USA
GELERNTER, JOEL, MD	PSYCHIATRY	YALE UNIVERSITY: CT, USA
GOLDBERG, JON, PHD	Biomaterials	
GRAVELEY, BRENTON, PHD	Genetics and Developmental	
GREENSTEIN, ROBERT, MD	Pediatrics/Genetics	
GRILLE, MICHAEL, BS	GCRC	
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	
HERMAN, AREY, BA	Psychiatry	
HERNANDEZ-AVILA, CARLOS, MD	Psychiatry	
HESELBROCK, VICTOR, PHD	Psychiatry	
HETTINGER, THOMAS, PHD	Oral Health & Diagnostic	
HULL, DAVID, MD	SURGERY	HARTFORD HOSPITAL: CT, USA
HUSSAIN, NAVEED, MD	Pediatrics	
IOANNIDOU, EFFIE, DDS	Periodontology	
ISOGNA, KARL, MD	INTERNAL MEDICINE	YALE UNIVERSITY: CT, USA
JOSEPH, CHERIAN, MD	Medicine/Geriatrics	
KADDEN, RONALD M, PHD	Psychiatry	
KAMINER, YIFRAH, PHD	Psychiatry	
KAPLAN, RICHARD, PHD	Psychiatry	
KAPTUCH, JUSTIN, BS	GCRC	
KELLY, JOHN R, DDS,DSC	Oral Rehab, Biomaterials	
KENNY, ANNE, MD	Center on Aging	
KERSTETTER, JANE, PHD	NUTRITION	UCONN - STORRS: CT, USA
KING, ANDREA, PHD	DEPT OF PSYCHIATRY	UNIVERSITY OF CHICAGO: IL, USA
KINGSBURY, JEFFREY, DDS,MD	Oral & Maxillofacial Surge	
KNOX, ISABELLA, MD	Pediatrics	
KOZLAK, SCOTT, BS	GCRC	
KRANZLER, HENRY, MD	Psychiatry	
KRAUSE, PETER, MD	Pediatrics	
KREUTZER, DONALD L, PHD	Pathology	
KUCHEL, GEORGE, MD	Center on Aging	
KURTZMAN, SCOTT, MD	Surgery	
LALANDE, MARC, MD	Genetics & Develop Biology	
LALLA, RAJESH, BDS,PHD	Oral Diagnosis	
LAMBRECHT, RICHARD, PHD	Pharmacology & Toxicology	
LAMMI, KEEFE, PHD	NUTRITION	UCONN, STORRS: CT, USA

LEVINE, JOEL, MD	Medicine	
LEWIS, COURTLAND, MD	Orthopedics	
LI, ZIHAI, MD,PHD	Ctr for Immunotherapy	
LITT, MARK, PHD	Behavioral Sci & Comm Hlth	
LORENZO, JOSEPH, MD	Medicine	
MADEJ, OLGA, BA	GCRC	
MALCHOFF, CARL, MD,PHD	Medicine/Endocrinology	
MALCHOFF, DIANA, PHD	Medicine	
MANSOOR, GEORGE, MD	Medicine/Hypertension	
MARKS, LAWRENCE, PHD	GENERAL MEDICINE	PIERCE FOUNDATION LABORATORY: CT, USA
MARTIN, ISHMAEL, MD	Pulmonary	
MAYER, BRUCE, PHD	Genetics & Dev. Biology	
MCELHANEY, JANET, MD	Immunology	
MEIERS, JONATHAN, DDS	Prosthodontics	
MENZOIAN, JAMES, MD	CTR FOR CLIN CARE IMPROV	
MEYER, JOHN, MD,PHD	Occupational Medicine	
MIRZA, FARYAL, MD	Medicine	
MOFFITT, KATHIE H, PHD	Psychiatry	
MOHLER, WILLIAM, PHD	Genetics & Dev. Biology	
MOYO, VICTOR, MD	Medicine/Oncology	
MUKHERJI, BIJAY, MD	Medicine	
NELLISSERY, MAGGIE, MD	Psychiatry	
NICHOLS, FRANK, PHD	Oral Health & Diag Science	
NICHOLS, GINGER, MS	Human Genetics	
O'CAMPO, PATRICIA, PHD	MATERNAL/CHILD HEALTH	U OF TORONTO, CANADA
ONCKEN, CHERYL, MD	Medicine	
ONYIUIKE, HILARY, MD	Neurosurgery	
PACHTER, LEE, MD	PEDIATRICS	INSTITUTE OF LIVING: CT, USA
PANZER, VICTORIA, MD	Neurology	
PAPPAGALLO, MARIANN, MD	Pediatrics	
PARHAM, KOUROSH, MD	Surgery	
PEARLSON, GODFREY, MD	PSYCHIATRY	INSTITUTE OF LIVING: CT, USA
PENDRYS, DAVID, DDS,PHD	Behavioral Sci & Comm Hlth	
PETERSON, DOUGLAS, DMD,PHD	Oral Diagnostics	
PETRY, NANCY, PHD	Psychiatry	
PHULWANI, PRIYA, MD	MEDICINE/ENDOCRINOLOGY	CONNECTICUT CHILDREN'S MEDICAL: CT, USA
PIERUCCI, AMIRA, PHD	Psychiatry	
PILBEAM, CAROL, MD,PHD	Medicine	
PRESTWOOD, KAREN, MD	Medicine	
PROTIVA, PETR, MD	GASTROENTEROLOGY	
RADOLF, JUSTIN, 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	
ROPER, NITIN, BS	GCRC	
ROSENKRANTZ, TED S, MD	Pediatrics	
ROSSON, ROBERT, MD	Medicine	
ROUNSAVILLE, BRUCE, MD	PSYCHIATRY	YALE UNIVERSITY: CT, USA
RUBIN, KAREN, MD	PEDIATRICS	CONNECTICUT CHILDREN'S MEDICAL: CT, USA
SALAZAR, JUAN, MD	Pediatrics	
SALERMO, EDWARD, MD	Medicine/Pulmonary	
SANDERS, MARILYN, MD	Pediatrics	
SARFARAZI, MANSOOR, PHD	Surgery	
SCHRAMM, CRAIG, MD	Pediatric Pulmonary	
SCOTT, DENISE, BS	GENETICS	HOWARD UNIVERSITY: DC, USA

SECOR, ERIC, MD	Immunology	
SEIP, RICHARD, PHD	PREVENTIVE CARDIOLOGY	HARTFORD HOSPITAL: CT, USA
SHAFER, DAVID, DMD	Behavioral Sci & Comm Hlth	
SILVERMAN, DAVID I, MD	Medicine	
SMARADOTTIR, AGNES, MD	Medicine/Hem-Onc	
SMILOWITZ, HENRY, MD	Diagnostic Imaging & Thera	
SMITH, JOANNE, MD	Medicine	
SONIS, STEPHEN T, DMD,DMSC	ORAL & MAXILLOFACIAL SURGE	DANA FARBER CANCER INSTITUTE: MA, USA
SPIRO, JEFFREY, MD	Surgery	
SPORN, JONATHAN, MD	CANCER CENTER	ST. FRANCIS HOSPITAL: CT, USA
SQUIER, RACHEL, DSC,DMD	Prosthodontics	
STEINBERG, KAREN, PHD	Psychiatry	
STEVENS, MICHAEL, PHD	OLIN CENTER	HARTFORD HOSPITAL: CT, USA
STEVENS, RICHARD G, PHD	Community Medicine	
SULLIVAN, BRIDGET, MD	ALLIED HEALTH SCIENCES	UCONN - STORRS: CT, USA
SULLIVAN, TAMI, PHD	FAMILY VIOLENCE RESEARCH A	YALE UNIVERSITY: CT, USA
SWEDE, HELEN, PHD	Community Medicine	
TANEV, KALOYAN, MD	Psychiatry	
TANNENBAUM, SUSAN, MD	Medicine/Hem-Onc	
TAXEL, PAMELA, MD	Medicine	
TAYLOR, ROBERT, MD	PHARMACOLOGY	HOWARD UNIVERSITY: DC, USA
TENNEN, HOWARD, PHD	Community Medicine	
THAPAR, MANISH, MD	Internal Medicine	
THOMPSON, PAUL, MD	PREVENTIVE CARDIOLOGY	HARTFORD HOSPITAL: CT, USA
THRALL, ROGER, PHD	Medicine/Pulmonary	
TROJIAN, THOMAS, MD	MEDICINE/FAMILY MEDICINE	ST. FRANCIS HOSPITAL: CT, USA
TURNER, GARY, MD	OB/GYN	NEW BRITAIN GENERAL HOSPITAL: CT, USA
VIDWANS, ANIRUDDHA, MD	Pediatrics	
WAGNER, JULIE, PHD	Behavioral Sci & Comm Hlth	
WALSH, KEVIN, BA	GCRC	
WALSH, STEPHEN J, SCD	Ctr for Biostatistics	
WARFIELD, SIMON, PHD	RADIOLOGY	BRIGHAM & WOMEN'S HOSPITAL: MA, USA
WARREN, NICHOLAS, PHD	Occupational Medicine	
WAYNIK, ILANA, MD	Pediatrics	
WEIGERT, JEAN, MD	RADIOLOGY	WOMEN'S IMAGING: CT, USA
WEINER, SCOTT, MD	OB/GYN	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
ZAKKO, LIAM, BA	GCRC	
ZARFOS, KRISTEN, MD	Surgery	
ZUCKER, AARON, MD	PEDIATRICS	CONNECTICUT CHILDREN'S MEDICAL: CT, USA

## SUBPROJECT DESCRIPTIONS

<b>SPID:</b>	0051	<b>PROTOCOL:</b>	51	<b>TYPE:</b>	RESEARCH	
<b>SHORT TITLE:</b>	COGA					
<b>LONG TITLE:</b>	Collaborative Study on the Genetics of Alcoholism					
<b>AIDS:</b>	N	<b>TOTALS</b>		<b>A</b>	<b>B</b>	<b>D</b>
		Inpatient		0	0	0
<b>START DATE:</b>	9/1/1993	Scatter Bed		0	0	0
Total # pts expected for entire study:	3,175	Outpatient		21	0	0
		Scatter RN Hours		0	0	0
		Offsite Visits		0	0	0
<b>RESEARCH BIONUTRITION</b>	N	<b>MULTICENTER STUDY</b>		Y		
<b>INFORMATICS CORE</b>	Y	<b>CLINICAL TRIAL</b>		N		
<b>BIostatistician</b>	N	<b>CORE LAB</b>		Y		
<b>ANCILLARIES ONLY</b>	N					

<b>INVESTIGATOR</b>	<b>DEPARTMENT</b>	<b>NON-HOST INSTITUTION: STATE, COUNTRY</b>
HESELBROCK, VICTOR PHD	Psychiatry	
BAUER, LANCE 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 April 1, 2007 to March 31, 2008 for the Collaborative Study on the Genetics of Alcoholism (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.

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.

### Data Collection and Phenotyping Studies / Results

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 [Kathryn Hayden, James Plouffe, and Jesse Wagner]. During the past year, Ms. Kathryn Hayden and Jesse Wagner 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), C-SSAGAs, and

neuropsychological testing protocols. Ms Hayden and McCarter served as the primary SSAGA/C-SSAGA editors.

James Plouffe served as the site's ERP technician and will continue in that capacity. Jesse Wagner, who was hired during this grant year, will also serve as a backup Enterprise Resource Planning (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 recently retired as a Professor at the University of Connecticut School of Social Work. Christine Ohannessian, Ph.D. is an associate 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.

The scope of work proposed for FY19 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 still lags somewhat, given the project was one FTE short staffed for much of the year; that vacancy was filled by Jesse Wagner. We will catch up with the recruitment of subjects now that Mr Wagner is fully trained.

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 FHAM for waves I-III is now complete.

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. 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. Work has also continued to examine 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%).

#### 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 at interview, 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 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.

#### Plans for 2008-2009

Personnel - The UConn site anticipates no vacancies in staffing and no personnel changes are anticipated for the coming year.

Subject recruitment - The UConn site will actively pursue recruiting for the wave IV assessment period. During the current year, UCONN staff has 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.

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 psychological and environmental factors as predictors of the initiation of drinking behavior among young adolescents [with Drs. Ohannessian and M Hesselbrock]. In addition, genetic association and linkage studies will be performed [in conjunction with the COGA Genetic Analysis committee], 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 associated with adolescent drinking behavior (versus alcohol diagnoses such as abuse or dependence). 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. The adult / parent sample has just undergone a genome wide association study (GWAS) through the NIH's Center for Inherited Diseases Research (CIDR). In the coming year, as examination of these findings increase, there are likely to be more candidate genes and SNPs identified as possible susceptibility genes for alcohol dependence and related conditions that can be explored in the offspring sample described above now being examined prospectively.

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.

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

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**SHORT TITLE:** Primary Cortisol Resistance

**LONG TITLE:** Primary Cortisol Resistance

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AIDS:	N	TOTALS	A	B	D
		Inpatient	0	0	0
<b>START DATE:</b>	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	Y	CLINICAL TRIAL	N
BIostatistician	N	CORE LAB	N
ANCILLARIES ONLY	N		

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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. This study closed in the General Clinical Research Center (GCRC) on 09/06/2007.

<b>SPID:</b> 0231	<b>PROTOCOL:</b> 231	<b>TYPE:</b> RESEARCH
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<b>SHORT TITLE:</b>	Familial Papillary Thyroid Carcinoma
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<b>LONG TITLE:</b>	Familial Papillary Thyroid Carcinoma
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	AIDS:	N	TOTALS	A	B	D
			Inpatient	0	0	0
<b>START DATE:</b>		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	Y	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:

The long term goal is identification of the gene(s) causing familial papillary thyroid carcinoma. We are currently sequencing gaps in the human genome project within the minimal region of the 1q21 containing the gene and sequencing candidate genes. Large new families are being categorized as to linkage region.

In the last year we have added 14 new subjects for a total of 96 subjects in all.

No changes in recruitment, no unexpected safety concerns, no new interim data, no changes in protocol.

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

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**SHORT TITLE:** Smoking and Pregnancy - CAP

**LONG TITLE:** Smoking and Pregnancy - CAP

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AIDS:	N	TOTALS	A	B	D
		Inpatient	0	0	0
<b>START DATE:</b>	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	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	
CAMPBELL, WINSTON MD	Obstetrics/Gynecology	
KRANZLER, HENRY 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:**

A paper of the final results of this study was submitted to Obstetrics and Gynecology this last year but rejected. We are resubmitting the paper to Journal of Maternal-Fetal medicine within the next month.

**SPID:** 0268      **PROTOCOL:** 268      **TYPE:** RESEARCH

**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
<b>START DATE:</b>	2/1/1999	Scatter Bed	0	0	0
Total # pts expected for entire study:	90	Outpatient	0	9	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	
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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 CCMC study participants: the General Clinical Research Center (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 University of Connecticut Health Center (UHC) and the Connecticut Children's Medical Center (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.

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

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**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
<b>START DATE:</b>	10/1/1989	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	
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**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:**

This study was terminated here at the University of Connecticut Health Center on 06-20-2007.

There were no changes to protocol, no safety concerns, no publications



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

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

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AIDS:	N	TOTALS	A	B	D
		Inpatient	0	0	0
<b>START DATE:</b>	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	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 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:**

There is one subject on long term follow up for this study, one patient is deceased as of 04/03/2007. There have been no safety concerns, no publications, there have been no changes to the protocol. This study remains closed to accrual, there is no recruitment plan.

<b>SPID:</b> 0286	<b>PROTOCOL:</b> 286	<b>TYPE:</b> 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
<b>START DATE:</b>	11/30/1996	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
KURTZMAN, SCOTT MD	Surgery	

#### 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/m<sup>2</sup> and 500 mg/m<sup>2</sup>, 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/m<sup>2</sup> 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:

3 patients are in long term follow-up and have no evidence of disease, no Adverse Events, no new primaries and begin seen annually for follow up. 4 patients have expired due to progression of disease. Please note that The Hospital of Central Connecticut is 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 General Clinical Research Center.



<b>SPID:</b> 0292	<b>PROTOCOL:</b> 292	<b>TYPE:</b> RESEARCH
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<b>SHORT TITLE:</b>	Cutaneous Immune Response in Lyme Disease and Secondary Syphilis
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<b>LONG TITLE:</b>	Cutaneous Immune Response in Lyme Disease and Secondary Syphilis
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AIDS:	N	TOTALS	A	B	D
			Inpatient	0	0
<b>START DATE:</b>	4/1/1999	Scatter Bed	0	0	0
Total # pts expected for entire study:	100	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	N	CORE LAB	N
ANCILLARIES ONLY	N		

INVESTIGATOR	DEPARTMENT	NON-HOST INSTITUTION: STATE, COUNTRY
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RADOLF, JUSTIN MD	Microbial Pathogenesis	
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SALAZAR, JUAN MD	Pediatrics	
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#### 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:

The number of subjects enrolled during the reporting period is 34.

The number of subjects enrolled since the initiation of the study is 372.

There have been no unexpected safety concerns during this reporting period

Specific Aim One. To further characterize the innate immune responses elicited by treponemal lipoproteins in human skin (already completed and closed enrollment).

Specific Aim Two. To further characterize the cutaneous immune response to *T. pallidum* in secondary syphilis lesions (already completed and published).

Specific Aim Three. To elucidate immune cell responses to *T. pallidum* and *B. burgdorferi* or its constituents (manuscript in preparation)

Specific Aim Four. To study how *T. pallidum* and *B. burgdorferi* or its constituents activate macrophages following uptake into phagosomal vacuoles (ongoing using blood samples from healthy volunteers).

Studies related to Specific Aim and Two are now completed and have been published. Work on Specific Aim Two is also completed and has been accepted for publication. Given our successes at the Cali site and the unanticipated wealth of new information

obtained from combined analysis of blood and skin blister fluids, Dr. Salazar has expanded the scope of this work and has obtained independent funding and Institutional Review Board (IRB) approval to continue his research activities in Cali. Studies for Specific Aims Three and Four will continue at the University of Connecticut Health Center (UCHC) and will use the isolated peripheral blood mononuclear cells (PBMC) system to assess monocyte, T cell, and dendritic cell responses to live spirochetes and spirochetal components. to elucidate the mechanisms and signaling pathways elicited during uptake by macrophages of *Borrelia burgdorferi* and opsonized *T. pallidum*.

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
<b>START DATE:</b>	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	N	CORE LAB	N
ANCILLARIES ONLY	N		

INVESTIGATOR	DEPARTMENT	NON-HOST INSTITUTION: STATE, COUNTRY
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ONCKEN, CHERYL MD	Medicine	
COONEY, JUDITH PHD	PSYCHIATRY	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:**

Two papers have been published off this data set. We are analyzing the body composition data and hope to have another paper submitted this year.

**SPID:** 0322      **PROTOCOL:** 322      **TYPE:** RESEARCH

**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
<b>START DATE:</b>	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:

The study did not recruit any new patients during the reporting period, as recruitment was completed in June of '05. There have been no safety concerns. The study closed in the General Clinical Research Center (GCRC) on 06/05/2007.

**SPID:** 0325      **PROTOCOL:** 325      **TYPE:** RESEARCH

**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	<b>TOTALS</b>	<b>TOTALS</b>		
				A	B	D
			Inpatient	0	0	0
<b>START DATE:</b>			Scatter Bed	0	0	0
			Outpatient	0	0	0
Total # pts expected for entire study:		100	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		

<b>INVESTIGATOR</b>	<b>DEPARTMENT</b>	<b>NON-HOST INSTITUTION: STATE, COUNTRY</b>
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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:**

It was not possible to enroll any subjects during the reporting period due to some questions raised by the Institutional Review Board (IRB) about our recruitment procedure. We have recently got the final approval from IRB, which is valid until May 15 2009. Although there are no safety concerns, the IRB needed some clarification of the protocol too. In between we were able to do cytokine enzyme linked immunosorbent assay (ELISA) with some frozen culture medium collected from a previous study's case samples. These will help us for our (near) future publication.



**SPID:** 0329      **PROTOCOL:** 329      **TYPE:** RESEARCH

**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	<b>TOTALS</b>	<b>TOTALS</b>		
				A	B	D
			Inpatient	0	0	0
<b>START DATE:</b>			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			

<b>INVESTIGATOR</b>	<b>DEPARTMENT</b>	<b>NON-HOST INSTITUTION: STATE, COUNTRY</b>
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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:

The 9 patients enrolled at the University of Connecticut Health Center (UCHC) are all alive and disease free. They are in the long term follow-up. There have been no safety concerns, no unanticipated problems, no changes to protocol.

This study is closed to accrual; 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 General Clinical Research Center (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	0
<b>START DATE:</b>	6/20/2000	Scatter Bed	0	0	0
Total # pts expected for entire study:	60	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	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:

No participants were enrolled for study A & B during the above time period. There have been seven 2 year follow up visits and sixteen 3 year follow up visits for studies A & B.

No participants have been enrolled or have had follow up visits for study C during the above time period.

There have been no unexpected safety concerns and no changes made to the protocol.

There have been no publications during the above-mentioned time period.



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

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**SHORT TITLE:** Genetics of Opioid Dependence**LONG TITLE:** Genetics of Opioid Dependence

AIDS:	N	TOTALS	A	B	D
		Inpatient	0	0	0
<b>START DATE:</b>	10/19/2000	Scatter Bed	0	0	0
Total # pts expected for entire study:	460	Outpatient	161	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
KRANZLER, HENRY MD	Psychiatry	
GELERNTER, JOEL MD	PSYCHIATRY	YALE UNIVERSITY, CT USA
HESSELBROCK, VICTOR PHD	Psychiatry	
ROUNSAVILLE, BRUCE 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 184 participants for this study between 4/1/07 and 3/31/08. We have recruited 767 subjects in the study since its initiation. Subject payment has changed from \$75 to \$100 for cases and from \$50 to \$75 for control subjects. We continue to recruit cases and controls in addition to our previous recruitment of sibling pairs and family trios.

A waiver to consent for the phone screening phase only was approved as well as minor changes to the phone screen itself. Breath alcohol reading is also now evaluated to ensure that participants are able to give informed consent. The protocol has been changed so that control subjects are now being recruited as matches to the affected subjects as opposed to simply recruiting a control sample of convenience.



and no outcomes to report at this early stage of the competitive-renewal project.

**SPID:** 0365      **PROTOCOL:** 365      **TYPE:** RESEARCH

**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
<b>START DATE:</b>	2/16/2001	Scatter Bed	0	0	0
Total # pts expected for entire study:	100	Outpatient	88	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	Y	
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:**

No new participants were enrolled in the Selenium and Vitamin E Cancer Prevention Trial (SELECT) in the report period. Two 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) sent us a prepared Fact Sheet regarding a new finding of risks associated with excessive multivitamin use. The Fact Sheet was submitted to the IRB and subsequent to approval was distributed to enrolled participants, who signed a document acknowledging receipt and who were given a copy of the document.

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

**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
<b>START DATE:</b>	12/1/2000	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	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
KURTZMAN, SCOTT MD	Surgery	

#### 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:

All have completed study and are in long term follow-up only.

The Hospital of Central Connecticut (THOCC): Four patients were enrolled at this site. Three are alive and well without adverse events (AEs), new primaries, or recurrence. The fourth patient had new lung cancer primary in 03/12/07 and is being treated accordingly. The patient did not have AEs or recurrence related to breast cancer.

The University of Connecticut Health Center (UCHC): Five patients were enrolled at this site. One patient expired due to metastatic disease. One other patient moved to Washington DC and has been lost to follow-up. The other patient with metastatic disease to the brain had surgery on 8/31/07 for a left cerebellar tumor and is now in follow-up. The last two patients are alive and well without AEs, new primaries, or recurrence.



**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
<b>START DATE:</b>	12/1/2000	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:**

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:**

Local Report:

University of Connecticut Health Center (UCHC): As of 2/13/08 One patient is alive with 3rd recurrence for which the patient is receiving non-study treatment. No long-term toxicity noted.

The Hospital of Central Connecticut (THOCC): As of 2/13/08, 5 patients are alive and well with no adverse events (AE's), no new primaries and no recurrence of disease.

<b>SPID:</b>	0381	<b>PROTOCOL:</b>	381	<b>TYPE:</b>	RESEARCH	
<b>SHORT TITLE:</b>	Malaria					
<b>LONG TITLE:</b>	Study of the Human Malaria Parasite Plasmodium Falciparum					
<b>AIDS:</b>	N	<b>TOTALS</b>		<b>A</b>	<b>B</b>	<b>D</b>
		Inpatient		0	0	0
<b>START DATE:</b>	2/1/2001	Scatter Bed		0	0	0
Total # pts expected for entire study:	17	Outpatient		12	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
BENMAMOUN, CHOUKRI MD	Microbial Pathology	
ELSHEICKA, HANY MD	Center for Microbial Patho	
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:**

1. Number of Subjects enrolled during the reported period: 8 subjects (15 blood draws)
2. Number of Subjects enrolled since initiation of the study: 35 subjects (144 blood draws)
3. Any changes in recruitment plans that might be needed: No
4. Unexpected safety concerns and their resolution: None
5. Interim data and outcomes if appropriate: None
6. Any proposed changes made or anticipated in the protocol. Enrollment was increased from 10 to 35 and was approved on 4/19/07.

<b>SPID:</b> 0399	<b>PROTOCOL:</b> 399	<b>TYPE:</b> RESEARCH
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<b>SHORT TITLE:</b>	NSABP- B33
<b>LONG TITLE:</b>	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	<b>TOTALS</b>			
				A	B	D
			Inpatient	0	0	0
<b>START DATE:</b>	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	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			

<b>INVESTIGATOR</b>	<b>DEPARTMENT</b>	<b>NON-HOST INSTITUTION: STATE, COUNTRY</b>
KURTZMAN, SCOTT MD	Surgery	

**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:**

University of Connecticut Health Center (UCHC) - 3 patients were enrolled into this study. All 3 patients are doing well. 2 patients are off study, one continues with Long Term Follow Up only. At last follow up (11-12-2007) patient was seen by Dr. Ann Waitzman and is alive and well.

The Hospital of Central Connecticut (THOCC) report: 2 patients enrolled since initiation of trial. One patient is deceased as of April 2006.

One patient was last seen 5/17/07 by Dr. Fallon, is still on treatment, no adverse events (AEs), recurrence, or new primaries. (Dr. Fallon). Receiving Exemestane (as approved by the Food and Drug Administration (FDA) on October 5, 2005); not receiving any experimental treatment.

<b>SPID:</b> 0400	<b>PROTOCOL:</b> 400	<b>TYPE:</b> RESEARCH
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<b>SHORT TITLE:</b>	NSABP-B34
<b>LONG TITLE:</b>	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
<b>START DATE:</b>	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	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:**

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:**

Locally: the University of Connecticut Health Center (UCHC) accrued 3 patients. All are alive and well and have not had recurrence. The Hospital of Central Connecticut (THOCC) accrued 2 patients. One is alive and well. The other patient is deceased as of 11/27/2007.

There have been 3 unexpected safety concerns with this study; however, they involved patients who were not enrolled in the National Surgical Adjuvant Breast and Bowel Project (NSABP) B34 study. There are no proposed changes to the protocol at this time. The Institutional Review Board (IRB) adverse event (AE) computer system reference numbers are: 3000, 3001, 3002.

<b>SPID:</b> 0410	<b>PROTOCOL:</b> 410	<b>TYPE:</b> RESEARCH
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<b>SHORT TITLE:</b>	Testosterone Effects on Bone and Frailty in Men with Osteoporosis
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<b>LONG TITLE:</b>	Testosterone Effects on Bone and Frailty in Men with Osteoporosis
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AIDS:	N	TOTALS	A	B	D
		Inpatient	0	0	0
<b>START DATE:</b>	10/15/2001	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	Y	CORE LAB	N
ANCILLARIES ONLY	N		

INVESTIGATOR	DEPARTMENT	NON-HOST INSTITUTION: STATE, COUNTRY
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KENNY, ANNE 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	A	B	D
		Inpatient	0	0	0
<b>START DATE:</b>	11/15/2001	Scatter Bed	0	0	0
Total # pts expected for entire study:	60	Outpatient	36	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	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 6 more subjects enrolled in the above time period. We closed the study for recruitment in the above time period. The data is currently being analyzed by a statistician and manuscript preparation is underway.

**SPID:** 0417      **PROTOCOL:** 417      **TYPE:** RESEARCH

**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
<b>START DATE:</b>	12/20/2001	Scatter Bed	0	0	0
Total # pts expected for entire study:	24	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
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:

4 subjects were enrolled in the study. There was no study activity in the reporting period. The study was terminated in the General Clinical Research Center (GCRC) on 12/25/07.

<b>SPID:</b> 0426	<b>PROTOCOL:</b> 426	<b>TYPE:</b> 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
<b>START DATE:</b>	11/4/2002	Scatter Bed	0	0	0
Total # pts expected for entire study:	10	Outpatient	7	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	Y	
ANCILLARIES ONLY	N			

INVESTIGATOR	DEPARTMENT	NON-HOST INSTITUTION: STATE, COUNTRY
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DIECKHAUS, KEVIN MD	Medicine/Infectious Diseases	
FRIEDLAND, GERALD MD	PSYCHIATRY	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/mm<sup>3</sup> -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 on July 11, 2007. No further follow-up is planned. Data from the trial has been presented and published. A final paper was published in the New England Journal of Medicine 355:2283-2296, 2006, which was reported in last year's annual report.



**SPID:** 0428      **PROTOCOL:** 428      **TYPE:** RESEARCH

**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
<b>START DATE:</b>	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	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 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-1β), 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 was accrued at The Hospital of Central Connecticut (THOCC). She is alive and well, no recurrences, Adverse Events (AE's) or new primaries.

The progress notes for this reporting period remain the same as those from the last: 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 General Clinical Research Center (GCRC).

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

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

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<b>AIDS:</b>	N	<b>TOTALS</b>	<b>A</b>	<b>B</b>	<b>D</b>
		Inpatient	0	0	0
<b>START DATE:</b>	4/25/2002	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	Y	CLINICAL TRIAL	N
BIostatistician	N	CORE LAB	N
ANCILLARIES ONLY	N		

<b>INVESTIGATOR</b>	<b>DEPARTMENT</b>	<b>NON-HOST INSTITUTION: STATE, COUNTRY</b>
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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:**

This study is in the process of competitive renewal. We did not recruit any subject in the last year. We were conducting analysis and going through renewal preparation.

<b>SPID:</b>	0442	<b>PROTOCOL:</b>	442	<b>TYPE:</b>	RESEARCH	
<b>SHORT TITLE:</b>	HALT-C Trial					
<b>LONG TITLE:</b>	The Hepatitis C Antiviral Long-Term Treatment Against Cirrhosis (HALT-C)					
<b>AIDS:</b>	N	<b>TOTALS</b>		<b>A</b>	<b>B</b>	<b>D</b>
		Inpatient		0	0	0
<b>START DATE:</b>	5/7/2002	Scatter Bed		0	0	0
Total # pts expected for entire study:	45	Outpatient		23	0	0
		Scatter RN Hours		0	0	0
		Offsite Visits		0	0	0
<b>RESEARCH BIONUTRITION</b>	N	<b>MULTICENTER STUDY</b>	Y			
<b>INFORMATICS CORE</b>	Y	<b>CLINICAL TRIAL</b>	Y	Phase III-IV		
<b>BIostatistician</b>	N	<b>CORE LAB</b>	Y			
<b>ANCILLARIES ONLY</b>	N					

<b>INVESTIGATOR</b>	<b>DEPARTMENT</b>	<b>NON-HOST INSTITUTION: STATE, COUNTRY</b>
BONKOVSKY, HERBERT MD	Medicine/Gastroenterology	
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 most are now in the Halt-C extension/observational part of the trial. The Data Safety Monitoring Board (DSMB) last met in June, 2007, and voted unanimously to continue the Halt-C Trial. There were no safety concerns identified. A total of 11 patients continue to be seen every six months at the University of Connecticut Health Center's (UCHC) General Clinical Research Center (GCRC). Other patients have died or been transplanted, have moved away, have elected to leave the study, or have elected to have continuing follow-up performed at another clinical center.

The main results of the Trial are that long-term, low-dose pegylated interferon is NOT of benefit in patients with advanced chronic hepatitis C. Rather, it is important for us to find better ways of treating and curing the chronic viral infection. This result was presented in Nov, 2007, at the annual meeting of the American Association for the Study of Liver Diseases, and the full paper describing the results has been submitted to The New England Journal of Medicine. We anticipate final acceptance of a revised version, but this cannot yet be guaranteed. There have been a number of publications that have appeared or been accepted during 2007--2008, all of which have cited the University of CT Health Center's GCRC, and all of which have already been transmitted to the Administrative Office of the GCRC [Lisa Godin and Lesley Mancini].

<b>SPID:</b> 0445	<b>PROTOCOL:</b> 445	<b>TYPE:</b> RESEARCH
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**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
<b>START DATE:</b>	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
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MAYER, BRUCE 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. Because of ongoing difficulties in recruiting subjects, and changing research priorities, this study was officially closed on 3/31/08.

<b>SPID:</b> 0448	<b>PROTOCOL:</b> 448	<b>TYPE:</b> RESEARCH
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<b>SHORT TITLE:</b>	Soy and Isoflavones
<b>LONG TITLE:</b>	The Effect of Soy Protein and Isoflavones on Bone on Older Women

	AIDS:	N	TOTALS			
				A	B	D
			Inpatient	0	0	0
<b>START DATE:</b>			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
KENNY, ANNE MD	Center on Aging	
KERSTETTER, JANE PHD	NUTRITION	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 General Clinical Research Center (GCRC) support for ongoing laboratory analysis and statistical assistance.

**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	<b>TOTALS</b>	<b>TOTALS</b>		
			<b>A</b>	<b>B</b>	<b>D</b>
		Inpatient	0	0	0
<b>START DATE:</b>	7/12/2002	Scatter Bed	0	0	0
Total # pts expected for entire study:	80	Outpatient	36	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		

<b>INVESTIGATOR</b>	<b>DEPARTMENT</b>	<b>NON-HOST INSTITUTION: STATE, COUNTRY</b>
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 4/1/2007 until 3/31/2008, 18 women enrolled. One was found to be ineligible during the first visit and excluded from participation, for a total of 17 eligible participants during this period. Since initiation of the study, 150 subjects have enrolled and 122 have been eligible and able to fully participate (25 women were excluded from the study after an Informed Consent Form (ICF) was collected 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 IRB this year include: 1) Hartford Hospital (HH) was removed as a collaborator on this study due to changes in their staff and inability to run subjects. All references to HH were removed. Dr. Paul Thompson was removed as a co-investigator. 2) Dr. Mallareddy completed her fellowship and is no longer employed by the University of Connecticut Health Center (UCHC). Dr. White (currently a co-investigator) took over her study responsibilities, 3) A change in protocol adding a mental stress challenge, additional flow mediated dilation assessments, and additional blood samples, 4) Change in Protocol for subset of participants for an Expressive Writing Intervention\*\*\*the General Clinical Research Center (GCRC) HAS

THIS UNDER A SEPARATE STUDY NUMBER 657, 5) Changes have been made to the ICF and protocol to reflect the above modifications. A separate ICF, Part B has been submitted for the Expressive Writing Intervention. This ICF is part of GCRC study 657. There were no unexpected safety concerns for this study

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**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
 

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AIDS:	N	<b>TOTALS</b>	<u>A</u>	<u>B</u>	<u>D</u>
		Inpatient	0	0	0
<b>START DATE:</b>	11/1/2002	Scatter Bed	0	0	0
Total # pts expected for entire study:	20	Outpatient	0	6	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		

<b>INVESTIGATOR</b>	<b>DEPARTMENT</b>	<b>NON-HOST INSTITUTION: STATE, COUNTRY</b>
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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.

During the report period, we will see the infants at their age three visits. One final visit will be done as part of the study at age four and one half. 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. There have been publications from the primary site referencing the study.



**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	<b>TOTALS</b>	<b>A</b>	<b>B</b>	<b>D</b>
			Inpatient	0	0
<b>START DATE:</b>	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		

<b>INVESTIGATOR</b>	<b>DEPARTMENT</b>	<b>NON-HOST INSTITUTION: STATE, COUNTRY</b>
TAXEL, PAMELA MD	Medicine	
LORENZO, JOSEPH 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:

Study is not actively recruiting

<b>SPID:</b> 0466	<b>PROTOCOL:</b> 466	<b>TYPE:</b> RESEARCH
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<b>SHORT TITLE:</b>	Nicotine Replacement Treatment (SNAP) Nicotine Replacement
<b>LONG TITLE:</b>	Nicotine Replacement Treatment for Pregnant Smokers

	AIDS:	N	<b>TOTALS</b>			
				A	B	D
			Inpatient	0	0	0
<b>START DATE:</b>		12/2/2002	Scatter Bed	0	0	0
Total # pts expected for entire study:		266	Outpatient	214	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	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 have randomized approximately 194 subjects enrolled in the randomized trial. A paper has been written and sent to Obstetrics and Gynecology for publication. We are awaiting a review.

The genetics substudy continues to run. We have recruited approximately 380 smokers and 200 never smokers. We also received de-identified samples from Duke University (about 140 new id's) depending on how many of these deoxyribonucleic acid (DNA) samples are useable, we are getting close to the goal of 565 pregnant smokers. We plan to recruit until Jan 2008 and conduct follow-ups until July 2009.

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

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

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AIDS:	N	<b>TOTALS</b>	A	B	D
		Inpatient	0	0	0
<b>START DATE:</b>	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	Y	CLINICAL TRIAL	N
BIostatistician	N	CORE LAB	N
ANCILLARIES ONLY	N		

<b>INVESTIGATOR</b>	<b>DEPARTMENT</b>	<b>NON-HOST INSTITUTION: STATE, COUNTRY</b>
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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	<b>TOTALS</b>			
				A	B	D
			Inpatient	0	0	0
<b>START DATE:</b>		10/23/2002	Scatter Bed	0	0	0
Total # pts expected for entire study:		900	Outpatient	3	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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KRANZLER, HENRY 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 3 participants for this study between 3/31/07 and 4/1/08. We recruited a total of 967 subjects (261 control and 706 affected individuals) in the study since its initiation. The study was closed to enrollment 4/2007. Data analysis still continues and we are in the process of applying for renewal.

**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
<b>START DATE:</b>	10/24/2002	Scatter Bed	0	0	0
Total # pts expected for entire study:	172	Outpatient	4	0	0
		Scatter RN Hours	0	0	0
		Offsite Visits	84	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 PHD	Psychiatry	
CARROLL, KATHLEEN PHD	PSYCHIATRY	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: 0

No changes in recruitment plans are needed (enrollment is complete).

- No unexpected safety concerns have occurred.
- Interim data and outcomes are not available.
- No changes were made to the protocol and none are anticipated.
- Results not yet published as study is ongoing.

Do you wish to continue to receive GCRC resources for the period April 1, 2008 through March 31, 2009? No, study is completed

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

**SHORT TITLE:** Mu-Opioid Receptor Polymorphism and HPA  
**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	0
<b>START DATE:</b>	10/17/2002	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	N	
INFORMATICS CORE	Y	CLINICAL TRIAL	Y	Phase II-III
BIostatistician	Y	CORE LAB	N	
ANCILLARIES ONLY	N			

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

- 1) Number of subjects enrolled during the report period: none. Since initiation of study: 43.
- 2) Planned changes in recruitment plans: The study has been closed for enrollment since November 2005, the last subject ended participation in December 2005.
- 3) Unexpected safety concerns and their resolution: None occurred.
- 4) Interim data: The OPRM1 Asn40Asp was unexpectedly found to associate with cortisol response only in subjects of European-American heritage. Large differences in genetic background may have large effects even on biologically functional genetic variants such as the Asn40Asp coding polymorphism. The results of this analysis have been published during the past year.
- 5) Proposed changes made or anticipated in the protocol: None.
- 6) Continued GCRC support requested - 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 Hypothalamic-pituitary-adrenal (HPA) axis.

<b>SPID:</b> 0471	<b>PROTOCOL:</b> 471	<b>TYPE:</b> RESEARCH
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**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 $\mu$ -Opioid Receptor Polymorphism and Hypothalamic-Pituitary-Adrenal (HPA) Axis Activation

AIDS:	N	TOTALS	A	B	D
		Inpatient	0	0	0
<b>START DATE:</b>	11/4/2002	Scatter Bed	0	0	0
Total # pts expected for entire study:	1,000	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	Y
ANCILLARIES ONLY	N		

INVESTIGATOR	DEPARTMENT	NON-HOST INSTITUTION: STATE, COUNTRY
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PROTIVA, PETR MD	GASTROENTEROLOGY	
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:

There were no subjects enrolled during the report period. There are a total of 142 subjects enrolled. 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

**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
<b>START DATE:</b>	12/10/2002	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	N
INFORMATICS CORE	Y	CLINICAL TRIAL	N
BIostatistician	N	CORE LAB	N
ANCILLARIES ONLY	N		

INVESTIGATOR	DEPARTMENT	NON-HOST INSTITUTION: STATE, COUNTRY
MAYER, BRUCE 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. In consultation with General Clinical Research Center (GCRC) staff and leadership, we have decided to transfer coordination of this study to the Neag Cancer Center. This will make more sense in terms of logistics, as Cancer Center staff and nurses are on the appropriate wards continuously and can identify and consent subjects more easily.

This study was closed in the GCRC as of 3/31/08.



**SPID:** 0478      **PROTOCOL:** 478      **TYPE:** RESEARCH

**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	<b>TOTALS</b>	<b>A</b>	<b>B</b>	<b>D</b>
			Inpatient	0	0
<b>START DATE:</b>	1/9/2003	Scatter Bed	0	0	0
Total # pts expected for entire study:	2,400	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	Y
ANCILLARIES ONLY	N		

<b>INVESTIGATOR</b>	<b>DEPARTMENT</b>	<b>NON-HOST INSTITUTION: STATE, COUNTRY</b>
PROTIVA, PETR MD	GASTROENTEROLOGY	
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:

There were no subjects enrolled during the current report period. There were 282 subjects enrolled since initiation.

There are no changes in recruitment plans that might be needed or unexpected safety concerns at this time.

Data analysis going on currently.

**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	A	B	D
		Inpatient	0	0	0
<b>START DATE:</b>	1/16/2003	Scatter Bed	0	0	0
Total # pts expected for entire study:	10	Outpatient	0	211	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 BDS, PHD	Oral Diagnosis	
DAMATO, KATHRYN L MS	Oral Diagnosis	
DANNENBERG, ANDREW J MD	GASTROENTEROLOGY/HEPATO LOG	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 the 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.

<b>SPID:</b> 0492	<b>PROTOCOL:</b> 492	<b>TYPE:</b> RESEARCH
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<b>SHORT TITLE:</b>	Keloid Formation
<b>LONG TITLE:</b>	Molecular Mechanisms for Keloid Formation

	AIDS:	N	TOTALS	A	B	D
			Inpatient	0	0	0
<b>START DATE:</b>			Scatter Bed	0	0	0
Total # pts expected for entire study:		50	Outpatient	76	0	0
			Scatter RN Hours	0	0	0
			Offsite Visits	53	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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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 as of 3/31/2008: 685

Current Year Enrollment: 124

Changes in recruitment plans: No changes needed.

Unexpected safety concerns and their resolution: None

Interim data and outcomes:

- We have enrolled 124 subjects during the reporting period.
- The General Clinical Research Center (GCRC)-sponsored pilot project for recruitment in Nigeria is highly successful.
- Preliminary mapping has been performed with a pilot grant from the GCRC.

Proposed changes made or anticipated in the protocol:

- We tested the families for consistency using Combined DNA Index System(CODIS) markers and for exclusion or linkage to published keloid loci on chromosomes 7 and 2.
- Hepatocyte Growth Factor (HGF) was tested for mutations.

We will need to test more families for consistency in the coming period.

Publications: None

<b>SPID:</b>	0494	<b>PROTOCOL:</b>	494	<b>TYPE:</b>	RESEARCH	
<b>SHORT TITLE:</b>	Open Angle Glaucoma					
<b>LONG TITLE:</b>	Molecular Screening of Optineurin Gene in Patients with Adult-Onset Primary Open Angle Glaucoma					
<b>AIDS:</b>	N	<b>TOTALS</b>		<b>A</b>	<b>B</b>	<b>D</b>
		Inpatient		0	0	0
<b>START DATE:</b>	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
<b>RESEARCH BIONUTRITION</b>	N	<b>MULTICENTER STUDY</b>		N		
<b>INFORMATICS CORE</b>	Y	<b>CLINICAL TRIAL</b>		N		
<b>BIostatistician</b>	N	<b>CORE LAB</b>		Y		
<b>ANCILLARIES ONLY</b>	N					

<b>INVESTIGATOR</b>	<b>DEPARTMENT</b>	<b>NON-HOST INSTITUTION: STATE, COUNTRY</b>
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- $\alpha$  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 a total of 180 blood samples were processed by the General Clinical Research Center (GCRC) Molecular Core Laboratory for Deoxyribonucleic Acid (DNA) extraction. Most of these were re-extraction of samples from patients that recruited into the study in the prior years.

The number of participating patients has generally 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. 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.





**SUBPROJECT PROGRESS:**

A total of 8 subjects were enrolled during the report period (a total of 192 since initiation of the study). Subject enrollment began in January 2003 and was completed in May 2007. Of the 192 subjects enrolled, 29 subjects were excluded and were not randomized to receive study drug (due to meeting exclusionary criteria, having out-of-range bloodwork results, or deciding not to participate).

A total of 163 subjects were randomly assigned to receive either naltrexone or placebo, administered on either a daily or a targeted basis. Of the 163 subjects randomized to study treatment, 138 (85%) completed treatment and 25 (15%) withdrew early (5 due to medication side effects, 7 due to lack of efficacy, and 13 due to other issues unrelated to study medication). The last treatment was delivered in August 2007 and the last follow-up assessment was completed in March 2008.

Follow-up data at 3 and 6 months post-treatment are available for 142 (87%) and 138 (85%) of patients, respectively. There were no unexpected safety concerns associated with this study. This study used interactive voice response technology (IVR) for daily data collection, with support from the General Clinical Research Center (GCRC). Compliance with the daily reporting of moods, events, drinking, and medication usage approached 90% of days for subjects while in the study, and was about 80% for all possible days, suggesting that data analysis will be able to proceed as planned.

Changes made in the protocol during the report period include the following: 1) addition of a statistician co-investigator (Grace Chan);

2) due to a letter from the Office of Human Research Protections (OHRP), the study protocol was reviewed and modified (where necessary) to cover the Deoxyribonucleic Acid (DNA)/genetic testing aspects of the study (including: an explanation of the purpose of the DNA testing aspects of this research study and a description of the DNA tests to be run on the collected samples; a description of any foreseeable risks and discomforts to the subjects regarding DNA testing; a description of any benefits to the subject or others that may reasonably be expected from the DNA testing; and a statement describing the extent to which the confidentiality of these records/samples identifying the subject will be maintained;

3) the protocol was modified to explain that DNA samples and phenotypic datasets will be de-identified before any examination of genetic markers for risk of alcohol dependence is resumed (and a notification will be sent to the IRB once all DNA samples and phenotypic data are completely de-identified);

4) protocol language was modified to reflect that women who become pregnant are withdrawn from the study;

5) removal of a co-investigator (Carlos Hernandez-Avila). There have been no recent publications associated with this study since data analysis is ongoing.

<b>SPID:</b>	0496	<b>PROTOCOL:</b>	496	<b>TYPE:</b>	RESEARCH	
<b>SHORT TITLE:</b>	Recurrent Lyme Disease					
<b>LONG TITLE:</b>	Recurrent Lyme Disease: Incidence, Pathogenesis and Clinical Outcome					
<b>AIDS:</b>	N	<b>TOTALS</b>		<b>A</b>	<b>B</b>	<b>D</b>
		Inpatient		0	0	0
<b>START DATE:</b>	5/15/2003	Scatter Bed		0	0	0
Total # pts expected for entire study:	5,000	Outpatient		289	0	0
		Scatter RN Hours		0	0	0
		Offsite Visits		0	0	0
<b>RESEARCH BIONUTRITION</b>	N	<b>MULTICENTER STUDY</b>		Y		
<b>INFORMATICS CORE</b>	Y	<b>CLINICAL TRIAL</b>		N		
<b>BIostatistician</b>	Y	<b>CORE LAB</b>		Y		
<b>ANCILLARIES ONLY</b>	N					

<b>INVESTIGATOR</b>	<b>DEPARTMENT</b>	<b>NON-HOST INSTITUTION: STATE, COUNTRY</b>
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:

1. The number of subjects enrolled during the report period was 290.
2. The number of subjects enrolled since initiation of the study has been 2587.
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 to the protocol during the reporting period; however, we are planning to submit National Institute of Health (NIH) grants for babesiosis and Lyme disease diagnostic studies and a babesia immunity study during the next reporting period. These will be collaborative studies with investigators from other universities. We plan to initiate pilot studies as part of these studies this summer.

**SPID:** 0497      **PROTOCOL:** 497      **TYPE:** RESEARCH

**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
<b>START DATE:</b>	3/6/2003	Scatter Bed	0	0	0
Total # pts expected for entire study:	112	Outpatient	98	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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LITT, MARK 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:

1. 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.

2. 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.

3. 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.

4. 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.

5. 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:

100 subjects have been enrolled, 12 since last progress report. Enrollment is now completed. 87% have provided posttreatment data, 80% have provided 6-month data, and 87% have provided 9-month data. There are no safety concerns. There are no interim data or outcomes available at this time. No publications have been prepared to date, but two are in preparation. One scientific presentation was made in March 2008. The General Clinical Research Center (GCRC) was cited as a contributor to this talk.

<b>SPID:</b> 0500	<b>PROTOCOL:</b> 500	<b>TYPE:</b> 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
<b>START DATE:</b>	7/1/2002	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 II-III
BIostatistician	N	CORE LAB	N	
ANCILLARIES ONLY	N			

INVESTIGATOR	DEPARTMENT	NON-HOST INSTITUTION: STATE, COUNTRY
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SALAZAR, JUAN 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:

Pediatric Acquired Immune Deficiency Syndrome (AIDS) Clinical Trial Group (PACTG) 390 (Version 3.0) has had a total enrollment of two subjects at the Connecticut Children's Medical Center since the initiation of the study. Both of these subjects have discontinued study participation as of Nov. 2007 due to the overall PACTG Site closure at Connecticut Children's Medical Center. The closing was due to non-refunding of the site.

This study has been closed to accrual.

There have been no unexpected safety concerns reported by The PACTG 390 team.

<b>SPID:</b> 0506	<b>PROTOCOL:</b> 506	<b>TYPE:</b> RESEARCH
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<b>SHORT TITLE:</b>	NSABP B-35
<b>LONG TITLE:</b>	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
<b>START DATE:</b>	1/30/2003	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 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:**

## Local Report:

University of Connecticut Health Center (UCHC): 5 patients were enrolled. Four patients are receiving study medication and are doing well with no evidence of disease. One patient discontinued study drug because of the side effects she was experiencing but did not withdraw her consent and is continuing with the quality of life questionnaire. This patient is alive and doing well.

The Hope Clinic: 2 patients were enrolled: One patient is still receiving study and doing well, was last seen on 04/21/2008. One patient drug was discontinued because she developed tuberculosis, which was unrelated to the study medication. This patient is also doing well

**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	<b>TOTALS</b>	<b>TOTALS</b>		
				A	B	D
			Inpatient	0	0	0
<b>START DATE:</b>		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	Y	CLINICAL TRIAL	N
BIostatistician	N	CORE LAB	N
ANCILLARIES ONLY	N		

<b>INVESTIGATOR</b>	<b>DEPARTMENT</b>	<b>NON-HOST INSTITUTION: STATE, COUNTRY</b>
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KENNY, ANNE MD	Center on Aging	
KUCHEL, GEORGE MD	Center on Aging	
MOHLER, WILLIAM 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 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.

<b>SPID:</b>	0514	<b>PROTOCOL:</b>	514	<b>TYPE:</b>	RESEARCH	
<b>SHORT TITLE:</b>	Congestive Heart Failure					
<b>LONG TITLE:</b>	Anabolic and Catabolic State of Adults with Congestive Heart Failure (CHF) According to Level of Frailty					
<b>AIDS:</b>	N	<b>TOTALS</b>		<b>A</b>	<b>B</b>	<b>D</b>
		Inpatient		0	0	0
<b>START DATE:</b>	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
<b>RESEARCH BIONUTRITION</b>	N	<b>MULTICENTER STUDY</b>		N		
<b>INFORMATICS CORE</b>	Y	<b>CLINICAL TRIAL</b>		N		
<b>BIostatistician</b>	N	<b>CORE LAB</b>		N		
<b>ANCILLARIES ONLY</b>	N					

<b>INVESTIGATOR</b>	<b>DEPARTMENT</b>	<b>NON-HOST INSTITUTION: STATE, COUNTRY</b>
KENNY, ANNE MD	Center on Aging	
BOXER, REBECCA MD	Medicine/Geriatrics	
HAGER, DAVID MD	Medicine/Cardio-Pulmonary	
MCELHANEY, JANET 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/height<sup>2</sup> (ASM/Ht<sup>2</sup>) 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/Ht<sup>2</sup>, 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/Ht<sup>2</sup>, 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/Ht<sup>2</sup>.

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/Ht<sup>2</sup>, 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 General Clinical Research Center (GCRC) statisticians for the project. Three manuscript preparations have been published from this work.

One manuscript in Osteoporosis International. Kenny AM, Boxer R†, Walsh S, Hager HD, Raisz LG. Femoral Bone Mineral Density in Patients with Heart Failure. Osteoporos Int. 2006;17(9):1420-7. Epub 2006 Jun 13. 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. 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 received Institutional Review Board (IRB) approval and will begin data collection this summer.

<b>SPID:</b>	0518	<b>PROTOCOL:</b>	518	<b>TYPE:</b>	RESEARCH	
<b>SHORT TITLE:</b>	Skeletal Disorders					
<b>LONG TITLE:</b>	Molecular Mechanisms for Skeletal Disorders					
<b>AIDS:</b>	N	<b>TOTALS</b>		<b>A</b>	<b>B</b>	<b>D</b>
		Inpatient		0	0	0
<b>START DATE:</b>	6/19/2003	Scatter Bed		0	0	0
Total # pts expected for entire study:	20	Outpatient		15	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		

<b>INVESTIGATOR</b>	<b>DEPARTMENT</b>	<b>NON-HOST INSTITUTION: STATE, COUNTRY</b>
REICHENBERGER, ERNST PHD	Biostructure and Function	

**SUBPROJECT DESCRIPTION:**

Craniometaphyseal dysplasia (CMD) is a monogenic craniotubular 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 as of 3/31/2008: 382

Current Year Enrollment: 12

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 Craniometaphyseal Dysplasia. Recruitment of human subjects is still ongoing. 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:

We used Luminex instrument to test samples for Tumor Necrosis Factor-alpha (TNF-alpha). In the future we would like to test more samples for TNF-alpha and Interleukin 6 (IL-6). Supplies will be provided by Reichenberger laboratory.

Publications (with mention of the General Clinical Research Center): 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	0
<b>START DATE:</b>	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	1,059	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 PHD	Psychiatry	
ALESSI, SHEILA 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: 437

Past Year Enrollment: 63

- 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.
- Results not yet published as study is ongoing.

Do you wish to continue to receive General Clinical Research Center (GCRC) resources for the period April 1, 2008 through March 31, 2009? Yes

**SPID:** 0523      **PROTOCOL:** 523      **TYPE:** RESEARCH

**SHORT TITLE:** Mif Genotyping  
**LONG TITLE:** Mif Genotyping and Osteoporosis

	AIDS:	N	<b>TOTALS</b>	<b>TOTALS</b>		
				A	B	D
			Inpatient	0	0	0
<b>START DATE:</b>		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	Y	CLINICAL TRIAL	N
BIostatistician	Y	CORE LAB	N
ANCILLARIES ONLY	N		

<b>INVESTIGATOR</b>	<b>DEPARTMENT</b>	<b>NON-HOST INSTITUTION: STATE, COUNTRY</b>
KENNY, ANNE 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 Macrophage Migration Inhibitory Factor (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 Bone Mineral Density (BMD) for those with any 5 allele (low expressing genotype) was  $0.89 \pm SD 0.13$  and for group with no 5 allele (high expressing genotype) was  $0.84 \pm SD 0.13$  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 General Clinical Research Center (GCRC) resources are required for continued data analysis and manuscript preparation.

<b>SPID:</b> 0524	<b>PROTOCOL:</b> 524	<b>TYPE:</b> RESEARCH
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<b>SHORT TITLE:</b>	Influenza Risk
<b>LONG TITLE:</b>	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
<b>START DATE:</b>	9/18/2003	Scatter Bed	0	0	0
Total # pts expected for entire study:	160	Outpatient	671	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 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:

Total number of subjects enrolled: 585  
 Number of subjects enrolled since last reporting period: 158  
 Changes in recruitment plan: no changes in recruitment plan at this time

Unexpected safety concerns and their resolution: no unexpected safety concerns occurred this past year

The study in question has three aims:

1) Establish causal relationships between changes in T-cell function and outcomes of influenza illness through a prospective study of older adults including those with congestive heart failure (CHF) and acute coronary syndromes (ACS). The hypothesis is that granzyme B (Grz B) is a key mediator of protection against influenza illness and is stimulated by a Th1 response to vaccination. With a defined threshold level of protection for GrzB and demonstrated low Th1 response (IFN-gamma:IL-10 ratio) to influenza, the next step is to determine the effect of different chemokines and cytokines on the response to influenza. The analysis is designed to produce a model of influenza risk based on prospectively measured GrzB and cytokine levels and the effect of clinical factors.

2) Elucidate mechanisms that alter the immune response to influenza and are associated with increased risk of influenza. The hypothesis is that influenza risk increases with the loss of the costimulatory molecule, CD28, and Grz B in influenza virus-specific CTL. A new hypothesis is that CD4+CD8+ T-cells become the reservoir for influenza-specific memory CTL with aging. FACS analysis will identify the cellular determinants that correspond to protection versus vaccine failure using the threshold level of GrzB as a correlate of protection following influenza vaccination. Similarly, microarray analysis will characterize the differences in gene expression with a protective vs. failed response to vaccination. The hypothesis that activation-induced cell death (AICD) determines the Th1:Th2 response has been abandoned due to recent evidence that T-cells must be conditioned in vitro to exhibit AICD. Thus, the effect of AICD is not a testable hypothesis under the ex vivo conditions of our assays.

3) Aim 3 has been modified to an alternate approach to enhancing the CTL response to influenza in older adults using costimulatory molecules. Our previous results suggest that efficacy in older adults may be improved with vaccines targeted to the CTL response. The hypothesis is that costimulatory molecules, 4-1BB ligand and CD70, will specifically increase the response to influenza-peptide CTL epitopes in older adults. FACS analysis will evaluate the virus-specific CTL frequency in virus or peptide-stimulated PBMC. Testing of heat shock proteins as potential vaccine adjuvants has been deferred until testing of co-stimulatory molecules has been completed.

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

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

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AIDS:	N	<b>TOTALS</b>	<u>A</u>	<u>B</u>	<u>D</u>
		Inpatient	0	0	0
<b>START DATE:</b>	9/25/2003	Scatter Bed	0	0	0
Total # pts expected for entire study:	20	Outpatient	2	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		

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<b>INVESTIGATOR</b>	<b>DEPARTMENT</b>	<b>NON-HOST INSTITUTION: STATE, COUNTRY</b>
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DONGARI-BAGTZOGLU, ANNA 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 did not recruit any subjects. Recruited human subjects at the General Clinical Research Center (GCRC) provide the blood/neutrophils used in in vitro experiments. We expect to recruit 10-15 subjects during the next year of funding by the National Institute of Health (NIH) (ROI was just renewed). There are no unexpected concerns or changes in the protocol. There were no publications related to human subjects during the last period.





<b>SPID:</b> 0529	<b>PROTOCOL:</b> 529	<b>TYPE:</b> RESEARCH
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<b>SHORT TITLE:</b>	Gaucher Registry
<b>LONG TITLE:</b>	Gaucher Registry

	AIDS:	N	<b>TOTALS</b>	<u>A</u> <u>B</u> <u>D</u>		
				Inpatient	0	0
<b>START DATE:</b>		11/20/2003	Scatter Bed	0	0	0
Total # pts expected for entire study:		40	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 IV
BIostatistician	N	CORE LAB	Y	
ANCILLARIES ONLY	N			

<b>INVESTIGATOR</b>	<b>DEPARTMENT</b>	<b>NON-HOST INSTITUTION: STATE, COUNTRY</b>
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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 principal investigator 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

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

	AIDS:	N	<b>TOTALS</b>	<b>TOTALS</b>		
				A	B	D
			Inpatient	0	0	0
<b>START DATE:</b>		10/16/2003	Scatter Bed	0	0	0
Total # pts expected for entire study:		44	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	Y
ANCILLARIES ONLY	N		

<b>INVESTIGATOR</b>	<b>DEPARTMENT</b>	<b>NON-HOST INSTITUTION: STATE, COUNTRY</b>
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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 TOTAL NUMBER OF PATIENTS ENROLLED:15

Current Year Enrollment: 0

Any changes in recruitment plans that might be needed No Unexpected safety concerns and their resolution No Interim data and outcomes if appropriate 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. However, the system stopped working for unclear reasons. The core lab has trouble amplifying products for sequencing. Still trouble shooting. Any proposed changes made or anticipated in the protocol No Publications N/A

<b>SPID:</b>	0531	<b>PROTOCOL:</b>	531	<b>TYPE:</b>	RESEARCH	
<b>SHORT TITLE:</b>	Sertraline Pharmacotherapy					
<b>LONG TITLE:</b>	Sertraline Pharmacotherapy for Alcoholism Subtypes					
<b>AIDS:</b>	N	<b>TOTALS</b>		<b>A</b>	<b>B</b>	<b>D</b>
		Inpatient		0	0	0
<b>START DATE:</b>	10/29/2003	Scatter Bed		0	0	0
Total # pts expected for entire study:	160	Outpatient		184	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 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 30 subjects were enrolled during the report period (a total of 123 since initiation of the study). As of 3/31/08, a total of 112 subjects had been randomized to receive treatment with either sertraline or placebo. We plan to run a recruitment ad specifically targeting individuals with early onset alcohol dependence, due to a difficulty in recruiting individuals in that group. 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 68% 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) Removal of a co-investigator (Carlos Hernandez-Avila) and addition of a new co-investigator (Carolyn Drazinic); 2) due to a letter from the Office of Human Research Protections (OHRP), the study protocol and consent form were reviewed and modified (where necessary) to cover the Deoxyribonucleic Acid (DNA)/genetic testing aspects of the research study (including: an explanation of the purpose of the DNA testing aspects of this research study and a description of the DNA tests to be run on the collected samples; a description of any foreseeable risks and discomforts to the subjects regarding DNA testing; a description of any benefits to the subject or others that may reasonably be expected from the DNA testing; a statement describing the extent to which the confidentiality of records/samples identifying the subject will be maintained); 3) the protocol and consent form were modified to explain that DNA samples will be kept in the laboratory until the study ends and that samples will then be de-identified (Due to the protocol and consent form modifications made for items #2 and 3, subjects who were active in the treatment phase of the study were re-consented at their next regularly scheduled appointment with the revised

consent form once it was IRB-approved. Prior to that, the research nurse reviewed the information regarding the DNA aspects of the study with active subjects and documented the discussion and date of discussion in subject's progress notes. Subjects were then asked to sign the revised consent form at their next visit once it was IRB-approved); 4) The IRB-approved consent form has always stated (since this study was originally IRB-approved), "My DNA will be studied to identify specific genetic markers that might influence my risk of alcohol dependence or my response to sertraline treatment." For consistency with the IRB-approved consent form, the protocol was updated to mention this specific aim of the study.

**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
<b>START DATE:</b>	11/25/2003	Scatter Bed	0	0	0
Total # pts expected for entire study:	18	Outpatient	54	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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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 are near completion of the study and we will soon start analysis of blood samples. The Institutional Review Board (IRB) has approved the study through January 2009.

We have 17 total completed subjects with 6 new since 4/1/2007. We have tried newspaper, broadcast e-mail, and other methods of recruitment but only get responses from the Broadcast E-mail message. There have been no unexpected safety concerns. No injury to participants has occurred. We have no interim data since the blood work is being batched analyzed at end of study. We will need to request an extension to the time frame. We have recruited 18 but 17 completed. One stopped due to time commitment. We are planning to have the lab analyze the bloods. No publications from this study have occurred, yet.

**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	0
<b>START DATE:</b>	12/1/2003	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	Y	CLINICAL TRIAL	N
BIostatistician	N	CORE LAB	N
ANCILLARIES ONLY	N		

INVESTIGATOR	DEPARTMENT	NON-HOST INSTITUTION: STATE, COUNTRY
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KRANZLER, HENRY 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 49 subjects were enrolled since the initiation of the study. This study has been closed to enrollment since December 2006 and is currently under secondary data analysis. Due to enrollment closure, there have not been any changes in recruitment plans. Further, there have not been any unexpected safety concerns within this report period.

During the report period, a protocol modification to address Deoxyribonucleic Acid (DNA) testing and DNA sample storage was Institutional Review Board (IRB) approved on 12/10/07. In response to a recent letter from office for human research protections (OHRP), the study protocol was modified to address the DNA/genetic testing aspects of the study. Therefore, the following elements were fully addressed in the protocol:

'b7 An explanation of the purpose of the DNA testing aspects of this research study and a description of the DNA test to be run on the collected samples

'b7 A description of any foreseeable risks and discomforts to the subjects regarding DNA testing

'b7 A description of any benefits to the subject or others that may reasonably be expected from the DNA testing

'b7 A statement describing the extent, if any, to which the confidentiality of these records/samples identifying the subject will be maintained.

The protocol was also modified to explain that all DNA samples and data sets will be completely de-identified in order to conduct the genetic analysis as planned. Genetic analyses will not be conducted with the samples until the de-identification is complete. A notification will be sent to the IRB once all DNA samples and phenotypic data are completely de-identified.

Additional genotyping is anticipated (use of the General Clinical Research Center (GCRC) Core lab), suggesting 28 samples with 10 markers each.

**SPID:** 0542      **PROTOCOL:** 542      **TYPE:** RESEARCH

**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
<b>START DATE:</b>	2/10/2004	Scatter Bed	0	0	0
Total # pts expected for entire study:	8	Outpatient	3	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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MIRZA, FARYAL MD	Medicine	
MOYO, VICTOR MD	Medicine/Oncology	
TANNENBAUM, SUSAN MD	Medicine/Hem-Onc	
TAXEL, PAMELA MD	Medicine	

#### 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:

There are 12 subjects enrolled so far since initiation of the study. 2 subjects did not complete the study and one withdrew due to the time commitment involved.

There were no subjects enrolled during the period of 4/1/07 to 3/31/08, although 2 of the subjects previously enrolled were active during the above study period.

A significant increase in the blood pressures as measured by 24 hour ambulatory blood pressure monitoring has been seen in the 8 subjects who have completed the study.

Measurement of the hormones of the renin angiotensin system including measurement of serum aldosterone, renin levels, angiotensin converting enzyme level and angiotensin 1 levels are anticipated to be added to the protocol to help understand the pathogenesis of the increase in blood pressure with aromatase inhibitor therapy.

An oral abstract has been accepted for presentation at the Endocrine Society Annual meeting in San Francisco in June 2008. The General Clinical Research Center (GCRC) has been cited in the abstract.





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

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

AIDS:	N	<b>TOTALS</b>	<b>A</b>	<b>B</b>	<b>D</b>
			Inpatient	0	0
<b>START DATE:</b>	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	47	0	0

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

<b>INVESTIGATOR</b>	<b>DEPARTMENT</b>	<b>NON-HOST INSTITUTION: STATE, COUNTRY</b>
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PETRY, NANCY PHD	Psychiatry	
BABOR, THOMAS 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: 104

Past Year Enrollment: 2

- No changes in recruitment plans are needed (enrollment is complete).
- No unexpected safety concerns have occurred.
- Interim data and outcomes are not available.
- Changes to protocol: 1) Added to the protocol a new recruitment site, Connecticut Renaissance West in Waterbury, CT. 2) Clarified the timing of the follow-up interviews in the Informed Consent Form and protocol by stating that the interviews will occur "about 1, 3, 6, 9, 12 and 18 months" from intake. 3) Added new recruitment poster.
- Results not yet published as study is ongoing.

Do you wish to continue to receive General Clinical Research Center (GCRC) resources for the period April 1, 2008 through March 31, 2009? No, study enrollment is completed

<b>SPID:</b> 0549	<b>PROTOCOL:</b> 549	<b>TYPE:</b> RESEARCH
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<b>SHORT TITLE:</b>	GABRA2
<b>LONG TITLE:</b>	Haplotype Association Study of the GABRA2 Gene and Alcohol Dependence in Project MATCH Subjects

	AIDS:	N	<b>TOTALS</b>	<u>A</u> <u>B</u> <u>D</u>		
				Inpatient	0	0
<b>START DATE:</b>	3/18/2004		Scatter Bed	0	0	0
Total # pts expected for entire study:		2,200	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		

<b>INVESTIGATOR</b>	<b>DEPARTMENT</b>	<b>NON-HOST INSTITUTION: STATE, COUNTRY</b>
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COVAULT, JONATHAN MD, PHD	Psychiatry	
GELERNTER, JOEL MD	PSYCHIATRY	YALE UNIVERSITY, CT USA
HESSELBROCK, VICTOR PHD	Psychiatry	
KRANZLER, HENRY 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:

- 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 National Institute of Health (NIH) alcohol treatment study 'Project Matching Alcoholism Treatments to Client Heterogeneity (MATCH)' several years ago as well as cases and controls collected at the University of Connecticut Health Center (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: Single Nucleotide Polymorphisms (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 Gamma-Aminobutyric Acid A Receptor, Gamma 1 (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. In a more recently completed analysis, we found that that the risk allele for both GABRA2 and GABRG1 genes was associated with a poorer response to psychological treatment in project MATCH.

5) Proposed changes made or anticipated in the protocol: None

6) We request the General Clinical Research Center (GCRC) protocol remain active with the potential request for additional genotyping of the study sample.



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. There was no new enrollment 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. At this time, there only publication that has resulted from this study is: Etiology of New-Onset Jaundice: How Often Is It Caused By Idiosyncratic Drug-Induced Liver Injury In The United States? (pdf) American Journal of Gastroenterology, Oct. 2006, © 2006 by Am. Coll. of Gastroenterology, however the GCRC was not cited on this publication.

**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
<b>START DATE:</b>	8/3/2004	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	Y	CORE LAB	N
ANCILLARIES ONLY	N		

INVESTIGATOR	DEPARTMENT	NON-HOST INSTITUTION: STATE, COUNTRY
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KENNY, ANNE MD	Center on Aging	
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PRESTWOOD, KAREN MD	Medicine	
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#### 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

<b>SPID:</b> 0558	<b>PROTOCOL:</b> 558	<b>TYPE:</b> RESEARCH
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**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
<b>START DATE:</b>	8/5/2004	Scatter Bed	0	0	0
Total # pts expected for entire study:	40	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	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 principal investigator (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 2 year recalls were finished and a final report was submitted to the sponsor.

There were two additional bulk crown failures this year, no unexpected safety concerns and no changes to protocol. Scanning electron microscopy and EDAX chemical analysis were used on four failed crowns to identify a likely failure mechanism.

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	<b>TOTALS</b>	<b>A</b> <b>B</b> <b>D</b>		
				Inpatient	0	0
<b>START DATE:</b>		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	Y	CLINICAL TRIAL	N
BIostatistician	N	CORE LAB	Y
ANCILLARIES ONLY	N		

<b>INVESTIGATOR</b>	<b>DEPARTMENT</b>	<b>NON-HOST INSTITUTION: STATE, COUNTRY</b>
TENNEN, HOWARD PHD	Community Medicine	
AFFLECK, GLENN PHD	Community Medicine	
ARMELI, STEPHEN PHD		PACE UNIVERSITY, NY USA
CILLESSEN, ANTONIUS PHD	PSYCHOLOGY	UCONN, STORRS, CT USA
CONNER, TAMLIN PHD	Psychiatry	
COVAULT, JONATHAN MD, PHD	Psychiatry	
DEHART, TRACY PHD	PSYCHOLOGY	LOYOLA, IL USA
DUFFY, VALERIE PHD	ALLIED HEALTH SCIENCES	UCONN, STORRS, CT USA
FORD, JULIAN PHD	Psychiatry	
GUNTHERT, KATHLEEN PHD	PSYCHOLOGY	AMERICAN UNIVERSITY, DC USA
HERMAN, AREY BA	Psychiatry	
KRANZLER, HENRY 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 benzodiazepine 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:

- 1) Number of subjects enrolled during the report period: none since initiation of study: 410
- 2) Planned changes in recruitment plans: none
- 3) Unexpected safety concerns and their resolution: None occurred.
- 4) Interim data: Polymorphisms in several genes have been examined. Results for two genes (SLC6A4 and HTR1B) have shown significant associations with clinically relevant behavioral phenotypes (stress related alcohol use, daily anxiety reactivity, and aggressive behaviors). Results from this work have been published in the past year. Results for two other genes (TPH1 and TPH2) did not show hypothesized association with alcohol use, the results of this analysis have been recently accepted for publication (Gacek et al).
- 5) Proposed changes made or anticipated in the protocol: None.

6) Continued GCRC support requested - We request the GCRC protocol remain active with the potential request for additional genotyping of the study sample.

<b>SPID:</b> 0562	<b>PROTOCOL:</b> 562	<b>TYPE:</b> 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	<b>TOTALS</b>	<b>TOTALS</b>		
				A	B	D
			Inpatient	0	0	0
<b>START DATE:</b>		8/19/2004	Scatter Bed	0	0	0
Total # pts expected for entire study:		960	Outpatient	21	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		

<b>INVESTIGATOR</b>	<b>DEPARTMENT</b>	<b>NON-HOST INSTITUTION: STATE, COUNTRY</b>
PROTIVA, PETR MD	GASTROENTEROLOGY	
BONKOVSKY, HERBERT MD	Medicine/Gastroenterology	
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 62 subjects have consented to this study, 58 of whom were deemed eligible after the baseline visit. During the current reporting period, 11 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. Out of four previously approved sites: 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, two sites: Hartford Hospital and Hebrew Health Care Inc. of Hartford, were closed. SUNY has screened 15 and enrolled 12 subjects. University of Rochester has screened 7 and enrolled 4 subjects. Hartford Hospital has screened 4, enrolled one subject and referred 11 subjects 7 of which have been enrolled at the University of Connecticut Health Center (UCHC). 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 UCHC.

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 modifications submitted to the IRB were administrative modifications; Dr. Bonkovsky's role in the study changed from principal investigator to co- investigator, now Dr. Petr Protiva serves as principal investigator, Dr Michael Grupka, Dr Paul Appleton, Kathleen Curley, and Thomas Kiely were added to the study staff, Laura Glynn was removed from the study. Due to a difficulty in the recruitment and enrollment of the study subject Hartford Hospital and Hebrew Health Care Inc. of Hartford, were closed as study satellite sites.

**SPID:** 0563      **PROTOCOL:** 563      **TYPE:** RESEARCH

**SHORT TITLE:** Substance Abuse Behavior  
**LONG TITLE:** Individual Differences and Long-Term Follow-Up of Substance Use Behaviors

	AIDS:	N	<b>TOTALS</b>	<b>TOTALS</b>		
				<b>A</b>	<b>B</b>	<b>D</b>
			Inpatient	0	0	0
<b>START DATE:</b>		9/16/2004	Scatter Bed	0	0	0
Total # pts expected for entire study:		210	Outpatient	105	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		

<b>INVESTIGATOR</b>	<b>DEPARTMENT</b>	<b>NON-HOST INSTITUTION: STATE, COUNTRY</b>
KING, ANDREA 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: Enrollment for the CSDP ceased in July 2006. Our final total for the study was 198 enrolled subjects. Of these 198 subjects, 190 completed all three required experimental sessions. At this time, two subjects have withdrawn from the study (1 subject for unstated reasons in 2/06 and another who passed away following her 2-Year Follow-Up interview) leaving 188 subjects 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 4/1/07 to 3/31/08, the CSDP successfully completed 171 of 171 of these interviews. In addition, at 12 and 24 months, subjects completed a more extensive annual follow-up, consisting of demographic and substance use updates and psychosocial measures completed via online survey as well as a brief diagnostic interview completed during a brief phone conversation. During this period, the CSDP completed 97 of 97 of these interviews. Overall, the CSDP reports a 100% follow-up rate during this reporting period and an impressive 99.05% follow-up rate for the duration of the entire study.

Proposed Changes to Protocol: No changes are proposed for this protocol

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**SPID:** 0568      **PROTOCOL:** 568      **TYPE:** RESEARCH
 

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**SHORT TITLE:** Chemotherapy Induced Thrombophilia**LONG TITLE:** Chemotherapy Induced Thrombophilia

AIDS:	N	TOTALS	A	B	D
		Inpatient	0	0	0
<b>START DATE:</b>	10/19/2004	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	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	
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SMARADOTTIR, AGNES MD	Medicine/Hem-Onc	
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**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:**

This study closed in the General Clinical Research Center (GCRC) as of April 30, 2007.

<b>SPID:</b>	0569	<b>PROTOCOL:</b>	569	<b>TYPE:</b>	RESEARCH	
<b>SHORT TITLE:</b>	Breaking the Cycle of Behavioral Health Problems					
<b>LONG TITLE:</b>	Breaking the Cycle of Behavioral Health Problems					
<b>AIDS:</b>	N	<b>TOTALS</b>		<b>A</b>	<b>B</b>	<b>D</b>
		Inpatient		0	0	0
<b>START DATE:</b>	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
FORD, JULIAN PHD	Psychiatry	
ABU-HASABALLAH, KHAMIS PHD	Psychiatry	
ALBERT, DAVID PHD	Psychiatry	
MOFFITT, KATHIE H PHD	Psychiatry	
STEINBERG, KAREN PHD	Psychiatry	
TANEV, KALOYAN MD	Psychiatry	
TENNEN, HOWARD PHD	Community Medicine	

#### SUBPROJECT DESCRIPTION:

The study is a randomized clinical trial 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 Affect Regulation Guide for Education and Therapy (TARGET) and Present Centered Therapy (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:

The study has been closed for recruitment during this reporting time. A total of 174 participants have been enrolled. All participants have completed study procedures including the daily phone calls to the interactive voice response system (IVR) operated by the General Clinical Research Center (GCRC). There have been no unexpected safety concerns and no modifications were submitted. Data analyses are currently being prepared. No publications have been completed at this time.

**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
<b>START DATE:</b>	9/30/2004	Scatter Bed	0	0	0
Total # pts expected for entire study:	108	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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DONGARI-BAGTZOGLU, ANNA 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 the University of Connecticut Health Center (UCHC) since initiation of the study, none during the last report period. This study continues to be closed to recruitment. There were no unexpected concerns or changes in plans/protocol. The following abstracts were accepted for presentation: Ioannidou E\*, Hull D, Burlison J, Dongari-Bagtzoglou AI. Relationship between chronic periodontitis and chronic organ transplant rejection". 2007 IADR meeting (Continental European and Israeli Divisions). Ioannidou E\*, Hull D, Burlison J, Dongari-Bagtzoglou AI. "Periodontitis is an independent predictor for elevated serum CRP levels in solid organ transplant recipient". 2007 AAP meeting.



**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
<b>START DATE:</b>	5/19/2005	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	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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BURKI, NAUSERWAN 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 CO<sub>2</sub> production (VCO<sub>2</sub>) to resting  $V_e$ , is decreased in COPD
3. Whilst the relationship VCO<sub>2</sub>/arterial PCO<sub>2</sub> in COPD is similar to normals, the relationship  $V_e$ /arterial PCO<sub>2</sub> is decreased.
4. VCO<sub>2</sub> is similar in normocapnic and hypercapnic COPD, but  $V_e$ /VCO<sub>2</sub> 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 PCO<sub>2</sub>.

#### SPECIFIC AIMS

1. In patients with normocapnic COPD, and in healthy normal subjects, measure resting  $V_e$ , VCO<sub>2</sub>, end-tidal CO<sub>2</sub> and anatomic deadspace (V<sub>dan</sub>) and alveolar deadspace (V<sub>d<sub>alv</sub></sub>) and examine the relationship amongst these parameters and in relationship to arterial PCO<sub>2</sub> (PaCO<sub>2</sub>).
2. In patients with hypercapnic COPD, measure resting  $V_e$ , VCO<sub>2</sub>, end-tidal CO<sub>2</sub>, PaCO<sub>2</sub>, V<sub>dan</sub> and V<sub>d<sub>alv</sub></sub> 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  $V_e$ , VCO<sub>2</sub>, and end-tidal CO<sub>2</sub> to approximate the effects of acute exacerbations of COPD on these parameters. Ventilatory failure is associated with an increased arterial PCO<sub>2</sub> (PaCO<sub>2</sub>). Arterial PaCO<sub>2</sub> is determined by the balance between CO<sub>2</sub> production and excretion from the body (VCO<sub>2</sub>). CO<sub>2</sub> production is known to be increased in obesity (1), during exercise (2), fever, and with high carbohydrate diets (3, 4).

The critical importance of CO<sub>2</sub> 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 CO<sub>2</sub> (VCO<sub>2</sub>) by the human body as a natural physiologic process: CO<sub>2</sub> 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 CO<sub>2</sub> is dependent on three factors: metabolism, blood carriage mechanisms (acid/base, buffering mechanisms), and pulmonary excretion.

Dietary factors which alter CO<sub>2</sub> production are due to the differences between carbohydrates and fat: in glycolysis, 1 mol of CO<sub>2</sub> is produced in regenerating 6 mol of ATP, whereas in non-esterified fatty acid metabolism 1 mol of CO<sub>2</sub> is produced for 8 mol of ATP. Thus CO<sub>2</sub> production is dependent on the balance between fat and glycogen oxidation, and can be influenced by dietary changes (3, 4).

CO<sub>2</sub> is carried in the blood as dissolved CO<sub>2</sub> and [HCO<sub>3</sub><sup>-</sup>] and is affected by the acid-base state. The excretion of CO<sub>2</sub> by the lungs is considered primarily a function of ventilation, and complete equilibration is assumed between the PCO<sub>2</sub> 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 PCO<sub>2</sub>.

**SUBPROJECT PROGRESS:**

We are currently continuing to study both normal (>60 years age) and COPD patients. We have completed studies in an additional 5 normal subjects, and 3 COPD patients. The data have not been analysed yet.

<b>SPID:</b> 0575	<b>PROTOCOL:</b> 575	<b>TYPE:</b> RESEARCH
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<b>SHORT TITLE:</b>	NSABP B39
<b>LONG TITLE:</b>	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	<b>TOTALS</b>			
				A	B	D
			Inpatient	0	0	0
<b>START DATE:</b>	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		

<b>INVESTIGATOR</b>	<b>DEPARTMENT</b>	<b>NON-HOST INSTITUTION: STATE, COUNTRY</b>
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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:**

There have been 0 patients accrued to this study. This study was closed here at UCHC as of 05-14-2008. There have been no safety concerns, no publications.

<b>SPID:</b> 0576	<b>PROTOCOL:</b> 576	<b>TYPE:</b> RESEARCH
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<b>SHORT TITLE:</b>	NSABP R04
<b>LONG TITLE:</b>	NSABP R04: Treatment with Two Chemotherapy Drugs Combined with Radiation Therapy for Patients with Rectal Cancer

	AIDS:	N	<b>TOTALS</b>	<b>TOTALS</b>		
				A	B	D
			Inpatient	0	0	0
<b>START DATE:</b>		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		

<b>INVESTIGATOR</b>	<b>DEPARTMENT</b>	<b>NON-HOST INSTITUTION: STATE, COUNTRY</b>
KURTZMAN, SCOTT MD	Surgery	

#### 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:

2 enrolled at The Hospital of Central Connecticut (THOCC) for which the University of Connecticut Health Center (UCHC) is the operating Institutional Review Board (IRB). There are no unexpected safety concerns and no anticipated changes to the protocol. The General Clinical Research Center (GCRC) is not cited in any publications.

<b>SPID:</b> 0577	<b>PROTOCOL:</b> 577	<b>TYPE:</b> RESEARCH
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<b>SHORT TITLE:</b>	NSABP B-38
<b>LONG TITLE:</b>	NSABP B38: A Phase III, Adjuvant Trial Comparing Three Chemotherapy Regimens in Women with Node-Positive Breast Cancer

	AIDS:	N	<b>TOTALS</b>	<b>TOTALS</b>		
				A	B	D
			Inpatient	0	0	0
<b>START DATE:</b>	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	Y	Phase III
BIostatistician	N	CORE LAB	N	
ANCILLARIES ONLY	N			

<b>INVESTIGATOR</b>	<b>DEPARTMENT</b>	<b>NON-HOST INSTITUTION: STATE, COUNTRY</b>
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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 Docetaaxel/Doxorubicin/Cyclophosphamide (TAC) (Arm I) or dose-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 its 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:

University of Connecticut Health Center (UCHC): 6 patients were enrolled: all 6 patients completed their therapy without complications and are currently in the follow-up phase. All of the patients are doing well and have no evidence of disease. The Hospital of Central Connecticut (THOCC): 4 patients were enrolled: 1 deceased beginning of March 2007; 3 finished treatment and are in follow-up phase. Patients are doing well otherwise.

**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
<b>START DATE:</b>	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 alone in prolonging DFS in women with node-negative breast cancer.

**SUBPROJECT PROGRESS:**

There have been 0 patients accrued to this study. This study was closed here at the University of Connecticut Health Center (UCHC) as of 05-14-2008. There have been no safety concerns, no publications.

<b>SPID:</b>	0581	<b>PROTOCOL:</b>	581	<b>TYPE:</b>	RESEARCH	
<b>SHORT TITLE:</b>	Changing ART Adherence Behavior					
<b>LONG TITLE:</b>	Changing Antiretroviral (ART) Adherence Behavior for HIV-related Morbidity and Mortality					
<b>AIDS:</b>	Y	<b>TOTALS</b>		<b>A</b>	<b>B</b>	<b>D</b>
		Inpatient		0	0	0
<b>START DATE:</b>	4/28/2005	Scatter Bed		0	0	0
Total # pts expected for entire study:	360	Outpatient		257	0	0
		Scatter RN Hours		0	0	0
		Offsite Visits		0	0	0
<b>RESEARCH BIONUTRITION</b>	N	<b>MULTICENTER STUDY</b>		N		
<b>INFORMATICS CORE</b>	Y	<b>CLINICAL TRIAL</b>		N		
<b>BIostatistician</b>	N	<b>CORE LAB</b>		Y		
<b>ANCILLARIES ONLY</b>	N					

<b>INVESTIGATOR</b>	<b>DEPARTMENT</b>	<b>NON-HOST INSTITUTION: STATE, COUNTRY</b>
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 theoryART 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:

At this time, the study is no longer recruiting participants nor is the study running LifeWindows sessions in clinic. The study is in the data analysis stage.

A total of 138 participants were recruited for the LifeWindows Study at the University of Connecticut Health Center (CHIP). Two Participants transferred within study clinics, and 11 participants were screened-out leaving 125 participants at UCHC to completed baseline.

#### Baseline Information

Study wide, 594 [125] active participants completed baseline measures. Condition assignment was 290 treatment arm [59] and 304 control arm [66].

Of these, 61% (361) [60%, 75] were male, 39% (229) [40%,50] female, and .7% (4) [0%, 0] were transgendered or intersexed. 26% (156) [26%, 32] were Latino, and in response to self-report items, 44% (262) [32%, 40] reported being Black, 24% (141) [34%, 42] White, 7% (40) [9%, 11] reported other or multiple races, and 25% (151) [26%, 32] reported solely Latino.

Routes of HIV infection varied, with the most common being heterosexual sex (39%, 232 [37%, 46]), followed by IDU (21%, 126 [14%, 18]) and MSM (14%, 85 [22%, 28]), while estimated date of diagnosis with HIV ranged from 1981 to 2006 within and across all clinics.

Participants, according to self-report, were predominantly heterosexual (73%, 431 [66%, 82]), with fewer reporting gay (19%, 112 [27%, 34]) or bisexual (7%, 39 [4%, 5]).

Over a quarter of the participants were employed at baseline (39%, 233 [42%,53]), with a small number finding medications hard or very hard to afford (7%, 42 [5%, 6]). Housing was fairly stable within this population, with 91% (538 [96%, 120]) reporting a relatively stable place to live. A small number were on a self-prescribed break from all or some of their medications at baseline (7%, 43 [3%, 4]), and almost half reported consistent use of a pillbox as a strategy to take medications (46%, 270 [40%, 50]).

Finally, active injection drug use (in the past month) was reported by 6% of participants (38 [3%, 4]) at baseline. In terms of overall functioning, the sample was generally comparable to other HIV-positive sample in functioning slightly below the national average in physical and mental health measures (SF8 = ~46 (sd=10) and ~43 (sd=12), respectively [45.8(sd=10.59) and 43.4(sd=12.54)].

Average adherence (across all individual HIV medications prescribed) at baseline was generally high, with 89% (sd= .25) of prescribed HIV medication pills taken per day averaged over the previous 3-days (90%, sd=23%), 86% (sd= .27) of prescribed HIV medications taken within the prescribed time-frame over the last 3-days (88%, sd=26%), and across participants the average for Visual Analog Scale reports of adherence at baseline was 88% (sd= 21% [92%, sd=17% ]). It is important to note that all continuous adherence measures at baseline were kurtotic and non-normally distributed. Determining the most representative metric and appropriate analyses for these outcomes is the focus of our first phase of data analyses.

In terms of barriers to adherence, across all sessions, an average of 12 (sd=6 [11, sd=5.49]) IMB-model based adherence-deficit areas were triggered by participant responses. For those in the treatment arm, the software program then would offer an opportunity to work on any of these individually triggered potential problem areas, and the average amount of time spent specifically within intervention activities within the selected area for improvement was 11 minutes at baseline session (sd=6 [9.30, sd=5.54 ]).

The total time commitment for completing a baseline LifeWindows session ranged between 24 minutes (sd=10.10 [7.20, sd=2.92 ]) for those in the control arm to 39 (sd= 14.58 [31, sd=9.16 ]) minutes for those in the treatment arm. Time commitments decreased from baseline to average 13 [21] minutes for control sessions (sd= 4.46 [sd=6.99 ]) and 25 [20] minutes for treatment arm sessions (sd= 8.39 [sd=4.85 ]), with about 9 [12] minutes (sd= 3.79 [sd=2.6 ]) spent specifically engaging in intervention activities.



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The only change made to our study protocol during this Progress Report timeframe was the addition of adherence study nurses for the purpose of collecting Resistance data. No other changes were made during this time period.

**SPID:** 0582      **PROTOCOL:** 582      **TYPE:** RESEARCH

**SHORT TITLE:** Brain Changes and Risk Factors

**LONG TITLE:** Brain Changes and Risk Factors

	AIDS:	N	<b>TOTALS</b>			
				A	B	D
			Inpatient	0	0	0
<b>START DATE:</b>		4/28/2005	Scatter Bed	0	0	0
Total # pts expected for entire study:		99	Outpatient	60	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
WOLFSON, LESLIE MD	Medicine/Neurology	
CALHOUN, VINCE 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 MD	PSYCHIATRY	INSTITUTE OF LIVING, CT USA
WAGNER, JULIE PHD	Behavioral Sci & Comm Hlth	
WARFIELD, SIMON 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:**

Data collected for the cohort in our sub-study have included standardized clinical blood pressures (BP), 24-hour ambulatory BPs, and the following vascular plasma biomarkers: C-reactive protein, lipoproteins, fibrinogen, plasminogen-activator inhibitor-1, glucose/insulin concentrations. We have been evaluating the relations among the various BP components and white matter lesion (WML) volume and ultrasound-derived carotid intimal-medial thicknesses.

Initial cross-sectional analyses have demonstrated that approximately 15% of the total sample had elevated WML volumes; no significant correlations between the clinic nor 24-hour BP values and WML volumes have been observed. However, there are moderate and statistically significant positive relations among both 24-hour mean and sleep systolic BP and carotid intimal-medial thickness. Follow-up ambulatory BP and vascular biomarkers have been obtained in approximately half of the original cohort at 2 years. Analyses of the relations among these parameters and the brain and vascular target organ involvement are pending completion of the cohort at this time period.

Mobility baseline data analysis is complete and 24 month data analysis has been progressing as data is collected. A manuscript is in preparation detailing the sensitivity and specificity of the baseline data based upon the measurement variables selected. A frailty measure has been developed and will be applied to all data analyses. Analyses of the relationships between mobility variables and MRI, Cognitive, Cardiovascular and other measures await completion of the respective preliminary data analyses in those areas.

We found significant inverse correlations between lesion burden in these WM regions and outcome measures of mobility. Logistic regression analysis indicated lesion burden in the SCC as the most significant regional predictor of low mobility performance. Another significant predictor was the body mass index. Voxel-based group analysis showed that independently of mobility status the most frequent WM damage occurred in periventricular areas within the anterior and posterior aspects of the corona radiata.

White matter hyperintensities (WMHs) on T2 weighted and FLAIR sequences are ubiquitous in older persons and although initially a nuisance, population-based studies have linked them with vascular disease risk factors, most notably hypertension. Limited pathologic data indicate that WMHs correspond to areas of poor white matter integrity with spongiosis, demyelination and glial proliferation. This description suggests non-specific tissue damage consistent with ischemia/infarction. Logic leads one to infer microvascular disease as the causative agent with ischemia/infarction of small areas of white matter resulting in the WMHs. The anatomy of the blood supply to deep hemispheric white matter supports this as it is derived from end arterioles, distal in the vascular tree and thus vulnerable to disruption. What makes this important is the increasing link of WMHs to the major geriatric syndromes including cognitive and mobility impairment and well as urinary dysfunction. Our analysis of lesion burden and mobility indicate that damage to motor pathways plays an important role in mobility impairment of elderly individuals. We believe that this indicates that for a significant fraction of older persons these lesions are playing a role in limiting their mobility. Furthermore we have comparable data for urinary function which is compromised by lesion burden in frontal white matter tracts. We are currently analyzing the effects of regional lesion burden on cognition but have already demonstrated that total white matter lesion burden is associated with diminished speed of executive function. Thus we have demonstrated that WMHs play a role in impaired mobility, urinary dysfunction and diminished cognitive power by limiting brain connectivity. Our approach differs from others in that we are utilizing the regional specificity of the lesions to characterize their effects on the functional capacity of older persons. We have also shown that vascular disease risk factors are related to carotid artery intima-media thickness but not to brain WMH burden.

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**SPID:** 0586      **PROTOCOL:** 586      **TYPE:** RESEARCH
 

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**SHORT TITLE:** Transposon-Based Functional Analysis  
**LONG TITLE:** Transposon-Based Functional Analysis of Malaria Genome
 

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AIDS:	N	<b>TOTALS</b>	A	B	D
		Inpatient	0	0	0
<b>START DATE:</b>	6/16/2005	Scatter Bed	0	0	0
Total # pts expected for entire study:	0	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		

<b>INVESTIGATOR</b>	<b>DEPARTMENT</b>	<b>NON-HOST INSTITUTION: STATE, COUNTRY</b>
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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:**

1. Number of Subjects enrolled during the reported period: 0
2. Number of Subjects enrolled since initiation of the study: 18 subjects (26 blood draws)
3. Any changes in recruitment plans that might be needed: No
4. Unexpected safety concerns and their resolution: None
5. Interim data and outcomes if appropriate: None
6. Any proposed changes made or anticipated in the protocol.

Study was closed on 1/23/2008

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**SPID:** 0587      **PROTOCOL:** 587      **TYPE:** RESEARCH

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**SHORT TITLE:** Nucleoside Transporters  
**LONG TITLE:** Nucleoside Transporters of Plasmodium Falciparum

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AIDS:	N	<b>TOTALS</b>	A	B	D
		Inpatient	0	0	0
<b>START DATE:</b>	6/16/2005	Scatter Bed	0	0	0
Total # pts expected for entire study:	25	Outpatient	14	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		

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<b>INVESTIGATOR</b>	<b>DEPARTMENT</b>	<b>NON-HOST INSTITUTION: STATE, COUNTRY</b>
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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 parasite survival with an eye toward future drug development.

**SUBPROJECT PROGRESS:**

1. Number of Subjects enrolled during the reported period: 6 subjects (7 blood draws)
2. Number of Subjects enrolled since initiation of the study: 20 subjects (40 blood draws)
3. Any changes in recruitment plans that might be needed: No
4. Unexpected safety concerns and their resolution: None
5. Interim data and outcomes if appropriate: None
6. Any proposed changes made or anticipated in the protocol. Enrollment was increased from 10 to 35 and was approved on 4/19/07.

**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	0
<b>START DATE:</b>	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	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
KENNY, ANNE 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 calciotropic hormones (directly with 25OHD and inversely with parathyroid hormone (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 have begun data analysis and submitted one paper for publication thus far. The paper is under review and the General Clinical Research Center (GCRC) has been cited. We plan further analysis and will continue to require biostatistical 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
<b>START DATE:</b>	7/20/2005	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	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 PHD	Behavioral Sci & Comm Hlth	
COONEY, NED 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:**

110 patients enrolled in the study thus far, 16 in this study period. Enrollment is complete. Follow-up rate is 87%. 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 at this time.



<b>SPID:</b> 0590	<b>PROTOCOL:</b> 590	<b>TYPE:</b> RESEARCH
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**SHORT TITLE:** Pregnancy Stress

**LONG TITLE:** Longitudinal Measurement of Work Stressors in Pregnancy

AIDS:	N	TOTALS	A	B	D
			Inpatient	0	0
<b>START DATE:</b> 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	45	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 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. 40 subjects were recruited in the first year

and an additional 30 recruited and completed at least one interview in the current reporting period. Data are collected on scannable questionnaire forms; initial data on the first 30 subjects has just been scanned and received. Analysis of data from the first 30 participants completing all four survey waves and for which data was scanned and entered into our database shows findings that are consistent with the hypotheses of the study and already of statistical significance, which was unexpected at this stage, but positive for the study.

Larger-than-expected changes in within-individual work effort (mean difference 2.2 units,  $p < 0.01$ ), work overcommitment (2.6 units,  $p < 0.001$ ) and a marginal difference in work rewards (1.6 units,  $P = 0.18$ ) from early pregnancy through to term or near-delivery are already seen in our preliminary analyses, with  $> 25\%$  of subjects still to complete the full set of questionnaires. Moreover, there are major significant differences by race/ethnicity in findings which are consistent with other work by the PI; these show very strong differences in self-rated job control, which is lower in blacks than whites despite equivalent or better educational attainment in blacks (from the initial questionnaires, for blacks, 8/8 in low control work vs 18/32 for whites;  $p = 0.012$  by chi-sq. Very limited data is yet available for birthweight, since  $< 50\%$  of subjects have reported back, but based on few data points this shows a high correlation with job control in blacks ( $r^2 = 0.83$ ) vs whites (0.06) which is also consistent with our data from other studies. Cortisol measurements will be run en masse by the GCRC lab and are not yet available for analyses. Overall, based on limited preliminary data we are seeing stronger evidence of changes in job characteristics across pregnancy than we had anticipated, and substantial racial/ethnic differences.

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 and analysis stages, no publications have yet been completed.

**SPID:** 0591      **PROTOCOL:** 591      **TYPE:** RESEARCH

**SHORT TITLE:** Depression and Endothelial Function in Postmenopausal 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
<b>START DATE:</b>	7/25/2005	Scatter Bed	0	0	0
Total # pts expected for entire study:	200	Outpatient	39	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 4/1/2007 until 3/31/2008, 19 participants enrolled. Since initiation of the study, 39 women have enrolled, and 38 have been fully eligible to participate. One woman was excluded from the study after 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. Modifications to the project approved by IRB this year include: 1) Approval of a new recruitment add targeting women with a history of depression. At this time, we have nearly completed enrollment of women without a history of depression, but still need approximately 40 women with a history of depression. 2) Approval of a new HIPAA form in accord with IRB's revision to language. 3) Removal of Dr. Mallareddy from the study. She has completed her fellowship and is no longer affiliated with the University of Connecticut Health Center (UHC). Dr. White has assumed her responsibilities. 4) Approval of a Dr. Gina Abbott as Principal Investigator Back up. 5) Approval of new Informed Consent Form (ICF) incorporating changes in language regarding storage of samples (we will no longer be storing samples beyond close of study), method of payment (The General Clinical Research Center (GCRC) requests checks be made out to "cash", and the addition of the GCRC Research Subject Advocate's (RSA's) phone number. There are no unexpected safety concerns.

<b>SPID:</b> 0592	<b>PROTOCOL:</b> 592	<b>TYPE:</b> RESEARCH
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<b>SHORT TITLE:</b>	Canker Sores
<b>LONG TITLE:</b>	Prevention of Recurrent Aphthous Stomatitis Using Vitamins

AIDS:	N	TOTALS	A	B	D
			Inpatient	0	0
<b>START DATE:</b>	7/28/2005	Scatter Bed	0	0	0
Total # pts expected for entire study:	120	Outpatient	398	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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LALLA, RAJESH 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: 52, and since initiation of the study: 147. No changes in recruitment plans are needed. There were no unexpected safety concerns. Interim data and outcomes: None. Proposed changes made or anticipated

in the protocol: None.

<b>SPID:</b>	0596	<b>PROTOCOL:</b>	596	<b>TYPE:</b>	RESEARCH	
<b>SHORT TITLE:</b>	Chlorhexidine and Localized Taste Stimulation					
<b>LONG TITLE:</b>	Effect of Chlorhexidine on Taste in Specific Regions of the Tongue in Humans					
<b>AIDS:</b>	N	<b>TOTALS</b>		<b>A</b>	<b>B</b>	<b>D</b>
		Inpatient		0	0	0
<b>START DATE:</b>	5/1/2005	Scatter Bed		0	0	0
Total # pts expected for entire study:	24	Outpatient		39	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
FRANK, MARION DMD	Oral Diagnosis	
FORMAKER, BRADLEY PHD	Oral Health & Diagnostics	
HETTINGER, THOMAS PHD	Oral Health & Diagnostic	
MARKS, LAWRENCE 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<sup>®</sup>, 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 Analysis of Variance (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:

This year we published one paper. The abstract follows.

Regional specificity of chlorhexidine effects on taste perception.  
Grover R, Frank ME.

Chlorhexidine (CHX) gluconate, a bitter bis-biguanide antiseptic, reduces the intensity of the salty taste of NaCl and bitter taste of quinine in humans.

This study addresses regional specificity of CHX's effects on taste. Perceptual intensity and quality were measured for separate taste bud containing oral loci innervated either by afferent fibers of cranial nerve (CN) VII or CN IX. Measurements were obtained following three 1-min oral rinses with either 1.34 mM CHX or water, the control rinse. CHX rinse reduced the intensity of NaCl more at the tongue tip and palate than at posterior oral sites. Thus, fungiform and palatal salt-taste receptors may differ from salt-taste receptors of the foliate and circumvallate taste papillae. The intensity of quinine.HCl was reduced equally by CHX at all sites tested but was frequently tasteless on the less sensitive anterior sites, suggesting quinine receptor diversity. In rodents, a portion of NaCl-taste receptors in the receptive field of CN VII is sensitive to the epithelial Na<sup>+</sup> channel blocker amiloride and a

portion is amiloride insensitive; all CN IX receptors are amiloride insensitive. The current results are the first to suggest that there may also be distinct, regionally specific populations of NaCl-taste receptors in humans.

**SPID:** 0598      **PROTOCOL:** 598      **TYPE:** RESEARCH

**SHORT TITLE:** DPH Project 1  
**LONG TITLE:** Cigarette Smoking and Effects on Infant/Child Health (Project 1)

AIDS:	N	<b>TOTALS</b>	<u>A</u>	<u>B</u>	<u>D</u>
			Inpatient	0	0
<b>START DATE:</b>	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		

<b>INVESTIGATOR</b>	<b>DEPARTMENT</b>	<b>NON-HOST INSTITUTION: STATE, COUNTRY</b>
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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 analyzed by Dr. Lalandes, lab, but their were questions regarding validity of the data. The General Clinical Research Center (GCRC) lab is now confirming this analyses. And finally, Hur data analyses is also underway. We hope to have this completed by august of 2008. 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.



<b>SPID:</b>	0599	<b>PROTOCOL:</b>	599	<b>TYPE:</b>	RESEARCH	
<b>SHORT TITLE:</b>	Genetics of Relapse Risk					
<b>LONG TITLE:</b>	Genetic Versus Phenotypic Markers of Relapse Risk					
<b>AIDS:</b>	N	<b>TOTALS</b>		<b>A</b>	<b>B</b>	<b>D</b>
		Inpatient		0	0	0
<b>START DATE:</b>	8/18/2005	Scatter Bed		0	0	0
Total # pts expected for entire study:	250	Outpatient		31	0	0
		Scatter RN Hours		0	0	0
		Offsite Visits		0	0	0
<b>RESEARCH BIONUTRITION</b>	N	<b>MULTICENTER STUDY</b>		N		
<b>INFORMATICS CORE</b>	Y	<b>CLINICAL TRIAL</b>		N		
<b>BIostatistician</b>	N	<b>CORE LAB</b>		Y		
<b>ANCILLARIES ONLY</b>	N					

<b>INVESTIGATOR</b>	<b>DEPARTMENT</b>	<b>NON-HOST INSTITUTION: STATE, COUNTRY</b>
BAUER, LANCE PHD	Psychiatry	
COVAULT, JONATHAN MD, PHD	Psychiatry	
GELERNTER, JOEL 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 3 of NIDA grant # R01 DA017666-01A2, "Genetic versus phenotypic markers of relapse risk". As described in our progress report for Years 1 and 2, the recruitment and screening of study participants began on or about February 1, 2006. As of March 13, 2008, we have successfully recruited and tested 96 patients. The current number of recruits is slightly behind our projected goal. We are now (March 2008) in the 32nd month (i.e., approximate mid-point) of a 60 month project and are only 29 subjects shy of recruiting 50% of the sample. We are not concerned about this minor shortfall because we are now beginning to recruit 50 subjects to fill a healthy group of non-drug-dependent subjects who will be demographically matched to the patients. The subjects forming this group can be acquired and completed easily because they are required to participate in one laboratory session only and are not followed over time (unlike the drug dependent groups). Thus, in a relatively short period of time, our recruitment total can jump from 96 to 146. We anticipate no difficulties in attaining our final recruitment goal.

<b>SPID:</b> 0600	<b>PROTOCOL:</b> 600	<b>TYPE:</b> RESEARCH
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<b>SHORT TITLE:</b>	DPH Project 2
<b>LONG TITLE:</b>	Impact of Maternal Smoking on Auditory Behavior in Infants and Nicotinic Cholinergic Receptor Activation

	AIDS:	N	<b>TOTALS</b>			
				A	B	D
			Inpatient	0	0	0
<b>START DATE:</b>		10/13/2005	Scatter Bed	0	0	0
Total # pts expected for entire study:		96	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
HUSSAIN, NAVEED MD	Pediatrics	
CAPRIGLIONE, ANTOINETTE MD	OB/GYN	NEW BRITAIN GENERAL HOSPITAL, CT USA
TURNER, GARY MD	OB/GYN	NEW BRITAIN GENERAL HOSPITAL, CT USA
WEINER, SCOTT MD	OB/GYN	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 (NBAS), 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:

Study: 78 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. Microarray analyses of cord tissue were done to study differential regulation of growth related genes. 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). The results of microarray studies were presented at the Eastern Society of Pediatric Research meeting in Philadelphia (March 2008) A manuscript based on the microarray findings in umbilical cord samples, was submitted to 'Pediatric Research' for publication. The journal has accepted it for publication and we expect to see it in their August 2008 issue.

Another manuscript based on the Brazelton findings is in preparation.

Placental cotinine levels have been analyzed and the data are being evaluated.

Further work is planned on studying the placental samples for genes of interest and collaborations with other researchers are being sought.

**SPID:** 0601      **PROTOCOL:** 601      **TYPE:** RESEARCH

**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
<b>START DATE:</b>	8/18/2005	Scatter Bed	0	0	0
Total # pts expected for entire study:	48	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	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 period: 3

Number of subjects enrolled in the study altogether: 4

Any changes in recruitment plans that might be needed: As per the Progress Report from last year, we contacted Dr. Andrew Salner, Director of the Radiation Oncology Program at Hartford Hospital, to obtain the assistance of his group in recruiting subjects for this study, and we received Institutional Review Board (IRB) approval for adding this site. We are now communicating with Dr. Kenneth Miller from the Cancer Center at Yale University School of Medicine to determine whether he and his radiation oncology colleagues would be willing and able to assist us in subject recruitment. If we find that Dr. Miller and his colleagues are willing to help with subject recruitment, we will seek and obtain the appropriate IRB approvals from Yale and the Uconn Health Center IRB's.

Unexpected safety concerns and their resolution: None to report.

Interim data and outcomes if appropriate: No data to report at this time as we continue to remain blinded to study treatment assignment.

Any proposed changes made or anticipated in the protocol. None

Publications: none

<b>SPID:</b> 0602	<b>PROTOCOL:</b> 602	<b>TYPE:</b> RESEARCH
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**SHORT TITLE:** Asthmaticus

**LONG TITLE:**  $\beta$ -Adrenergic Receptor Polymorphisms: Implications for the Treatment of Status Asthmaticus in Children

AIDS:	N	TOTALS	A	B	D
			Inpatient	0	0
<b>START DATE:</b>	11/17/2005	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	Y	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  $\beta$ 2-adrenergic receptor have important effects in modulating responses to therapy for asthma. We propose to investigate the influence of a patient's  $\beta$ 2-adrenergic receptor genotype on the clinical response to  $\beta$ 2-AR agonist therapy during acute severe asthma exacerbation in children.

The overall objective is to assess the influence of a patient's  $\beta$ 2-adrenergic receptor ( $\beta$ 2-AR) genotype on the clinical response to  $\beta$ 2-AR agonist therapy. Our hypothesis is that children admitted with status asthmaticus who are homozygous for the Gly16 allele of the  $\beta$ 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  $\beta$ 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:

There are two arms to this trial, a prospective arm and a retrospective arm. The retrospective arm to this trial was added by Institutional Review Board (IRB) addendum on February 28, 2006 and was approved by the General Clinical Research Center (GCRC) Advisory Committee (GAC) on March 30th, 2006. Currently 74 children have enrolled in the prospective arm and 37 children have enrolled in the retrospective arm. The retrospective arm of this trial is completed and now closed. In the prospective arm, we plan to enroll 90 children over a 3 year period. Enrollment in the prospective arm began on December 28th, 2005 and should complete enrollment in the Fall of 2008. The core laboratory at the General Clinical Research Center (GCRC) has successfully able to obtain genotype results on all patients enrolled in the study.

There have been no safety concerns with this study. Nor are there any proposed changes or anticipated changes in the protocol or in the recruitment plans.

In the retrospective arm, since the previous report, we have enrolled an additional 5 patients into this study (now n=37). The addition of these subjects did not change the results of this study. Children with the Gly/Gly genotype had significantly shorter ICU length of stay, duration of continuous albuterol therapy, and were significantly less likely to require IV  $\beta$ 2-AR therapy than children with other  $\beta$ 2-AR genotypes. We concluded that a child's  $\beta$ 2-AR genotype significantly affected that child's response to acute  $\beta$ 2-AR agonist therapy. An abstract summarizing these findings was presented at the American College of Chest Physicians International Meeting in October 2007. Support and funding from the GCRC was 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.

In the prospective arm, since the previous report, we have enrolled an additional 27 patients into this study (now n=74). This

enrollment was slower than expected due to a milder than expected asthma season with less children requiring ICU admission. However, we continue to plan on completing enrollment this Fall, following the Spring 2008 and Fall 2008 asthma seasons. At interim analysis, genotyping data is available for 67 of these 74 children. Thus far, at amino acid position 16, fifteen (22%) children had the Gly/Gly genotype, six (61%) children had the Arg/Arg genotype, and forty-one (61%) children were heterozygous (Arg/Gly). There were also similar admission severity of illness between in these two groups of children as quantified by admission MPIS. However, those children with the Gly/Gly genotype had significantly shorter ICU length of stay and duration of supplemental oxygen therapy when compared to those with Arg/Gly or Arg/Arg genotypes. This supports the findings in the retrospective arm of this trial.

**SPID:** 0604      **PROTOCOL:** 604      **TYPE:** RESEARCH

**SHORT TITLE:** Mental Illness  
**LONG TITLE:** Trauma and Severe Mental Illness: II. Randomized Clinical Trial

AIDS:	N	TOTALS	A	B	D
		Inpatient	0	0	0
<b>START DATE:</b>	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
FORD, JULIAN 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:

One participant has been enrolled in this study since 4/1/07. A total of 20 participants have been enrolled since the start of the study, and is currently closed to enrollment. All of the participants have completed treatment and follow-up interviews. The interactive voice response system (IVR) component operated by the GCRC has also been completed by all study participants. The UCHC IRB has approved the study until 11/10/08. At the next continuation, a request will be made for expedited review for data analyses only.

There have been no unexpected safety concerns in the past year, however, there was one serious adverse event reported to the UCHC IRB due to a study participant being hospitalized for psychiatric reasons. This was an expected event due to the population that was included for enrollment.

There was an addendum included with the last continuation for approval of the John Dempsey release of information form to be stamped by the IRB to allow for communication with staff from the partial hospital program (PHP). This allowed for communication with the PHP staff regarding referring individuals for the study and to be able to communicate necessary information without breaking confidentiality.

The data are currently being prepared for analyses. No outcomes are ready to be reported at this time. There have been no publications, but hopefully this data will provide significant results that will facilitate future grants and enable us to further include those that have mental illness and substance use issues and are also coping with past traumatic experiences to research and provide treatment.

**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
<b>START DATE:</b>	12/14/2005	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	Y
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:

No subjects were enrolled during the report period. 44 subjects were enrolled since the initiation of the study. There are no unexpected safety concerns. Data analysis has been completed.

We had baseline data on 44 subjects. 54% of subjects had an elevated Cardiac CRP, 77% of subjects had an elevated fibrinogen, 52% of subjects had elevated brachial flow mediated dilation (FMD). Waist circumference correlated with area under the curve of glucose ( $r=0.428$ ). BMI correlated with systolic blood pressure ( $r=0.448$ ) and with TSH ( $r=0.441$ ). Triglycerides correlated with markers of insulin {AUC-I ( $r=0.650$ ), AUC-G ( $r=0.493$ ), HOMA-R ( $r=0.487$ ), QuickI ( $r=-0.482$ ) and ISI ( $r=-0.602$ )}.

29 subjects completed the 16 week study. Metformin did not produce any changes when compared to placebo. Change in absolute levels of 25 hydroxyvitamin D correlated positively with fibrinogen ( $r=0.705$ ), positively with triglycerides ( $r=0.701$ ), negatively with peak FMD ( $r=-0.738$ ) and negatively with HOMA-R ( $r=-0.576$ ). The percentage change in AST from baseline correlated negatively with the percentage change in CIR 30 ( $r=-0.544$ ). ( $p<0.01$  for all correlations).

Conclusions: Cardiometabolic abnormalities are common in obese hyperinsulinemic adolescents. We found correlations between markers of obesity, insulin resistance, cardiovascular disease and non-alcoholic fatty liver disease. TSH correlated with BMI suggesting that there may be some subclinical hypothyroidism in this group. An increase in Vitamin D levels was associated with a decrease in insulin resistance but an increase in cardiovascular disease markers.



There are no publications to date. The study is closed.

<b>SPID:</b> 0610	<b>PROTOCOL:</b> 610	<b>TYPE:</b> RESEARCH
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<b>SHORT TITLE:</b>	Zonisamide versus Placebo
<b>LONG TITLE:</b>	Zonisamide versus Placebo in the Treatment of Alcohol Dependence

AIDS:		TOTALS	A	B	D
	N	Inpatient	0	0	0
<b>START DATE:</b>	1/19/2006	Scatter Bed	0	0	0
Total # pts expected for entire study:	50	Outpatient	62	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 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 15 subjects were enrolled during the report period (a total of 24 since initiation of the study). As of 3/31/08, a total of 20 subjects had been randomized to receive treatment with either zonisamide or placebo.

We have not changed the recruitment plans, and are not planning any changes, although we did modify the advertisements in order to clarify that counseling is offered as part of study participation. 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) addition of Dr. Carolyn Drazinic as a co-investigator (change made to the Informed Consent Form (ICF) as well), 2) a revised Health Insurance Portability and Accountability Act (HIPAA) form was added, 3) The protocol and ICF were modified to add the rare/uncommon (but expected) possible adverse effects of paresthesia and taste perversion, 4) a new subject handout was added that illustrates standard drinking and educates the patients on non-hazardous drinking. All of these modifications have been approved by the IRB.

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**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

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AIDS:	N	TOTALS	A	B	D
		Inpatient	0	0	0
<b>START DATE:</b>	1/23/2006	Scatter Bed	0	0	0
Total # pts expected for entire study:	90	Outpatient	213	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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ONCKEN, CHERYL MD      Medicine

**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:**

71 subjects screened and 53 subjects have been randomized to treatment. Our goal is 60 subjects randomized to treatment. We have not analyzed any data.

**SPID:** 0612      **PROTOCOL:** 612      **TYPE:** RESEARCH

**SHORT TITLE:** Alcohol Challenge

**LONG TITLE:** Alcohol Effects on Subjective and Physiological Responses

AIDS:	N	TOTALS	A	B	D
		Inpatient	0	0	0
<b>START DATE:</b>	2/16/2006	Scatter Bed	0	0	0
Total # pts expected for entire study:	100	Outpatient	234	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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COVAULT, JONATHAN MD, PHD	Psychiatry	
ARIAS, ALBERT MD	Psychiatry	
KRANZLER, HENRY 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  $\alpha$ -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:

- 1) Number of subjects enrolled during the report period: 90 Since initiation of study: 156.
- 2) Planned changes in recruitment plans: Study enrollment expected to be complete by end May 2008.
- 3) Unexpected safety concerns and their resolution: There have been no unexpected safety concerns associated with this study and no serious adverse events. Approval was requested and received from the IRB for subject 612-086's to repeat 2nd lab session due to an alcohol dosing error by the pharmacy (problem reported to the Institutional Review Board (IRB)).
- 4) Interim data: none to date, awaiting completion of study.
- 5) Proposed changes made past year or anticipated in the protocol: Cheryl Oncken and Grace Chen were added as co-investigators. IRB approved Principal Investigators (PIs) request to increase in enrollment to 200 subjects on 8/13/07. Approval was requested to conduct a brief pre-screening visit for initial medical eligibility and to obtain saliva for genetic inclusion testing. This could occur off site (especially those at UCONN Storrs campus). IRB approved on 9/10/07. Approval was requested to add an additional specific aim #3, investigation of genetic variation in other candidate genes beyond GABRA2 and between subject differences in alcohol response. Several other genes are emerging from literature reports as being related to alcohol effects or alcohol dependence. Protocol and ICF were modified to address this change. Protocol was also modified to correct the current IRB approved enrollment number. IRB approved on 11/5/07. Request made to IRB and approved for increase in potential number of study completers to 80 (from 60) in the event a larger than anticipated number of subjects complete all 3 monthly lab sessions.

IRB approved January 2008 - A recruitment web site URL - [www.uchcalcoholstudy.com](http://www.uchcalcoholstudy.com) (refer to study #1) - was added to all recruitment materials for this study. The PI purchased a short easy to remember URL [www.uchcalcoholstudy.com](http://www.uchcalcoholstudy.com) for a site that we may use to link interested potential participants to our study brochure, ICF and contact information contained in a separate web page.

6) Continued General Clinical Research Center (GCRC) support requested - We request the GCRC protocol remain active, resource needs - GCRC clinic exam room for alcohol lab session, GCRC nursing/research assistant support for alcohol lab sessions, core lab for DNA isolation and genotyping.

**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
<b>START DATE:</b>	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	1,710	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 PHD	Psychiatry	
ALESSI, SHEILA PHD	Psychiatry	

#### 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: 131

Past Year Enrollment: 65

No changes in recruitment plans are needed.

- No unexpected safety concerns have occurred.
- Interim data and outcomes are not available.
- Changes to protocol: 1) Removed Tressa Hanson as study coordinator and contact. Danielle Barry and Ellen Ciesielski were added as study coordinator and study contact, respectively. Sean Sierra and Shanelle Carmichael were added as consenters and Todd Olmstead was added as co-investigator. 2) Clarified description of when the Service Utilization questionnaire (SU) is administered (at baseline and at each follow-up interview). 3) Expanded the description of the payment for urine samples submitted to include other small items up to \$3 in value (e.g., toiletries, snacks, bus tokens, etc.) in addition to gift certificates in the protocol and Informed Consent Form (ICF). 4) Revised the description of standard treatment in the protocol because we have observed that clinics vary on whether group therapy is mandated. 5) Clarified the form of payment for interviews by adding the words "in gift certificates" for the baseline assessment and "check" for the follow-up assessments in the protocol. 6) Removed two outdated references to the Substance Dependence Severity Scale (SDSS) in the protocol. 7) Clarified that FileMaker is used in conjunction with Excel and SPSS for data in the protocol. 8) Added a Methadone Treatment History Questionnaire. 9) Three questions added to the Addiction Severity Index regarding Medical Status and Drug/Alcohol Use. 10) A comments Box added to the bottom of page 2

of the Brief Symptom Inventory to document any discussion regarding suicidal or homicidal ideation if needed for potential adverse events records. 11) Additional codes and spaces were added to the Service Utilization in order to improve the accuracy of data collection and questions regarding visits with parole officers were also added. 12) Removed outdated phone number from one recruitment flyer.

- Results not yet published as study is ongoing.

Do you wish to continue to receive GCRC resources for the period April 1, 2008 through March 31, 2009? Yes

**SPID:** 0614      **PROTOCOL:** 614      **TYPE:** RESEARCH

**SHORT TITLE:** Vitamin D Deficiency  
**LONG TITLE:** Vitamin D deficiency in children with cerebral palsy

	AIDS:	N	<b>TOTALS</b>			
				A	B	D
			Inpatient	0	0	0
<b>START DATE:</b>			Scatter Bed	0	0	0
Total # pts expected for entire study:		100	Outpatient	26	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
YIGIT, SEVKET MD	PEDIATRICS	CONNECTICUT CHILDREN'S MEDICAL, CT USA
KENNY, ANNE 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 62 subjects were enrolled in the study since the initiation. There are no changes in the recruitment plan. There are no unexpected safety concerns. There are no anticipated changes in the protocol. There are no publications based upon the current study yet.

We analyzed the data of 62 subjects and submitted the findings as an abstract to the Annual Meeting of American Society for Bone and Mineral research. The abstract including the available data is as follows:

Is Vitamin D deficiency more common in children with cerebral palsy than in healthy children?  
 S.Yigit, B. McKinney, J.Pedersen, B.Draheim, F.Sylvester

Children with cerebral palsy (CP) may be at higher risk for vitamin D(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. Therefore, we hypothesized that children with CP have a higher prevalence of vit D deficiency than their unaffected siblings. To test this hypothesis, we measured serum 25 (OH) vit D (RIA, Immunodiagnostic Systems Ltd, Fountain Hills, AZ) levels in children with CP and their unaffected, healthy siblings living in the same household. Seasonal differences were examined. Vit D deficiency was defined as serum level <15 ng/ml and vit D insufficiency as serum level < 20 ng/mL based on previously published pediatric studies. 31 children with CP and 31 healthy siblings as controls between ages of 6 -18 years were enrolled. 12.9 % of children with CP were vit D deficient while 29 % of the siblings were deficient. Vit D insufficiency was found in 29 % of children with CP and 38.7 % of healthy siblings. Only 20 % of the children with CP and 13 % of healthy siblings had 25 (OH) vit D level of more than 30 ng/ml, a level considered as optimal. While the mean 25 (OH) vit D levels were low on both groups, healthy siblings had a significantly lower 25 (OH) vit D levels compared to the children with CP (mean 25 (OH) vit D level for children with CP  $24.5 \pm 12.9$ , healthy siblings  $19.6 \pm 8.4$ ,  $p=0.04$ ). Low vit D levels were more prevalent in healthy siblings during winter season (mean 25 (OH) vit D level for children with CP  $33.2 \pm 16.5$ , healthy siblings  $19.8 \pm 8.8$ ,  $p=0.01$ ). 80 % of the healthy siblings were consuming < 1 serving of milk per day. 58.8 % of the children with CP who had sufficient vit D levels were on supplemental tube feedings. Only one CP patient with vit D deficiency was on tube feedings but was on a ketogenic diet. None of the healthy siblings were taking vit D supplements while only 2 children with CP were on multivitamin supplements. Vit D deficiency/ insufficiency appear to be a prevalent public health care problem in both children with CP and healthy children. Although children with CP have higher risk factors, healthy siblings seem to have a higher prevalence of vit D deficiency/ insufficiency. Children with CP who are on tube feedings are less likely do develop vit D deficiency/ insufficiency. Healthy children may need counseling for prevention.

**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
<b>START DATE:</b>	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	Y	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 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 14 of GCRC funding, statistical analyses for this project were essentially complete (except for minor refinements) and a manuscript was in preparation. 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 15 of GCRC funding, but the resources required (primarily, time from Biostatistics Core staff) will be minimal.

<b>SPID:</b>	0618	<b>PROTOCOL:</b>	618	<b>TYPE:</b>	RESEARCH	
<b>SHORT TITLE:</b>	Girls in Recovery					
<b>LONG TITLE:</b>	Girls in Recovery from Life Stress (GIRLS)					
<b>AIDS:</b>	N	<b>TOTALS</b>		<b>A</b>	<b>B</b>	<b>D</b>
		Inpatient		0	0	0
<b>START DATE:</b>	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		

<b>INVESTIGATOR</b>	<b>DEPARTMENT</b>	<b>NON-HOST INSTITUTION: STATE, COUNTRY</b>
FORD, JULIAN PHD	Psychiatry	
ABU-HASABALLAH, KHAMIS PHD	Psychiatry	
ASTUR, ROBERT PHD	OLIN CENTER	HARTFORD HOSPITAL, CT USA
MOFFITT, KATHIE H PHD	Psychiatry	
STEINBERG, KAREN PHD	Psychiatry	
STEVENS, MICHAEL 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:

Thirty three participants have been enrolled in the GIRLS study since 4/1/07. A total of 70 have been enrolled since the beginning

of the study. Nine did not meet eligibility requirements at the time of the baseline interview. A total of 61 participants will be included in the data analysis. The GIRLS study closed for recruitment at the end of February, 2008. Funding for the study is provided by the Office of Juvenile Justice and Delinquency Prevention (OJJDP) through the end of August, 2008. This will provide the study staff with completing follow-up interviews. Thirteen girls are currently receiving the counseling component of the study. We expect a total of 15 girls to begin making their final round of phone calls to the interactive voice response (IVR) system operated by the GCRC within the next 3 months.

Modifications that were approved in the past year included changes in study personnel, re-assenting of girls that would allow for the GIRLS study staff to communicate with staff where the girls were recruited in order to help with scheduling appointments, the study safety procedures were modified as requested by the Department of Children and Families (DCF) to allow for a streamlined protocol in the event that a girl presents with suicidal ideation, the protocol for screening a participant was modified to include asking the parent/guardian permission before screening was done, some of the study forms were updated and modified, one measure (traumatic events screening inventory TESI) was modified to include specific ages of trauma occurrence, recruitment material was modified to reflect new changes as was the consent form and protocol, the consent form was modified to reflect the reduction of follow-up interviews from 3 to 2 if time point of the end date of the study did not allow for the final interview to be done, the treatment completion window was extended to allow for clinician/participant vacations, illnesses, or other activities that may come up, a reduction in the time period for the final follow-up interview was modified from 6 months to 4 to allow for all girls that were consented to complete the 3 study interviews, and recently we submitted a modification to be able to complete the post-treatment and follow-up interview in the participant's home. This will allow for increased number of interviews to be completed.

There have been no unexpected safety concerns in the past year, but there have been 10 adverse events concerning suicidal ideation, one participant was arrested at her residential facility for assaulting a staff member, two girls were sent to detention from their residential facility for aggressive behavior, and two girls went AWOL from their residential facility. A report to DCF was made because a GIRLS study participant reported to a study clinician that her friend (also a GIRLS study participant) told her that her stepfather was sexually abusing her. Five serious adverse events occurred regarding hospitalization for suicidal behavior. All of these events were reported to the UCHC and DCF IRB, as well as to the review board for the Court Support Services Division (CSSD).

The data are currently being prepared for analyses. No publications have been completed at this time.

<b>SPID:</b>	0619	<b>PROTOCOL:</b>	619	<b>TYPE:</b>	RESEARCH	
<b>SHORT TITLE:</b>	DA1c					
<b>LONG TITLE:</b>	Subjective and Physiological Effects of Alcohol: Role of Genetic Variation and Adrenal Hormones					
<b>AIDS:</b>	N	<b>TOTALS</b>		<b>A</b>	<b>B</b>	<b>D</b>
		Inpatient		0	0	0
<b>START DATE:</b>	3/28/2006	Scatter Bed		0	0	0
Total # pts expected for entire study:	20	Outpatient		269	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
COVAULT, JONATHAN MD, PHD	Psychiatry	
ARIAS, ALBERT MD	Psychiatry	
BAUER, LANCE PHD	Psychiatry	
FEINN, RICHARD PHD	Psychiatry	
KRANZLER, HENRY MD	Psychiatry	
NICHOLS, FRANK PHD	Oral Health & Diag Science	
PIERUCCI, AMIRA PHD	Psychiatry	

#### SUBPROJECT DESCRIPTION:

Alcohol has multiple pharmacological effects, though which of these effects relate to the risk of alcohol dependence is not clear. Family-based and case-control genetic studies of alcohol dependence indicate that genetic variations of the GABAA gene, GABRA2, influence the risk of developing alcohol dependence. Preliminary results from our alcohol laboratory studies in humans suggest that variation in GABRA2 influences the subjective effects of alcohol. Animal studies indicate that the neuroactive steroid allopregnanolone is an alcohol-modulated endogenous agonist at GABAA receptors and that genetic variation in steroid 5 $\alpha$ -reductase type I gene which generates neuroactive steroids, may moderate alcohol effects. Studies in humans have identified a functional  $\mu$ -opioid receptor polymorphism (Asn40Asp) that moderates the feedback regulation of the HPA axis and may be associated with variation in the neurosteroid response to acute alcohol. To better define the role of GABRA2 gene variation, neuroactive steroids and genetic variants of 5 $\alpha$ -reductase and  $\mu$ -opioid receptor genes on the acute effects of alcohol in humans, we propose to conduct a laboratory study of non-alcohol dependent drinkers using a 4-session design in which alcohol/placebo beverage is paired with dutasteride/placebo pretreatment. Dutasteride, an inhibitor of both type I and type II 5 $\alpha$ -reductase enzymes, blocks the production of 5 $\alpha$ -reduced neuroactive steroids. This study will extend our preliminary findings with finasteride by including a) a placebo control for alcohol, b) a more specific inhibitor of both 5 $\alpha$ -reductase isoenzymes, c) a larger group of subjects (including both light and heavy drinkers), d) quantitative tests of static ataxia and response inhibition, e) plasma concentrations of neuroactive steroids and their adrenal steroid hormone precursors at several time points following alcohol administration, and f) the effects of polymorphisms in steroid 5 $\alpha$ -reductase enzymes and  $\mu$ -opioid receptor genes on acute alcohol effects (including changes in levels of neuroactive steroids).

#### SUBPROJECT PROGRESS:

- 1) Number of subjects enrolled during the report period: 26 Since initiation of study: 26
- 2) Planned changes in recruitment plans: We will explore during the next year the feasibility of conducting the alcohol lab sessions at the Storrs campus for the Spring 2009 semester.
- 3) Unexpected safety concerns and their resolution: There have been no unexpected safety concerns associated with this study and no serious adverse events. Due to a pharmacy error in providing a lower dose of alcohol, one subject was asked and agreed to repeat one of the lab sessions.
- 4) Interim data: Limited examination of data from first 15 completers currently underway. Dutasteride found to have expected reduction in subjective responses to alcohol, but with greatest effect in 5 subjects who were classified as heavy drinkers.
- 5) Protocol changes made past year or anticipated:

IRB Approved on 4/12/2007: Question 13a was added to the phone screener to help determine subject's eligibility based upon availability for completion of the study visits. Questions 27c and 27d were added to carefully screen for alcohol dependence, and

questions 30a and 30b were added to carefully screen for drug abuse. Protocol was modified to add alcohol expectancies questionnaire to baseline data collection. The Informed Consent Form (ICF) was modified to include the following description of lab sessions: "In such an event, you would receive payment for that session but may or may not be invited back for any additional drinking sessions based on decision of study investigator." ICF was modified to include the following description of time of sessions: "This study requires a total of nine visits over a period of approximately 14-16 weeks: 1 screening visit, 4 lab sessions (scheduled about 1 month apart), and 4 "pre-lab sessions" (which take place 2-4 days before the lab sessions)." Dr. Cheryl Oncken was added as co-investigator. Certificate of Confidentiality (COC) was added to the study. Recruitment materials were modified to further clarify study details concerning visits and consumption of alcohol and medication.

IRB Approved on 5/30/2007: The header for all recruitment materials was modified from "Recruiting Healthy Research Volunteers" to a more specific header "Healthy Adult Men Needed for Alcohol Study". The study protocol was modified to include an additional brief cognitive test - GMLT. This test adds 4-5 minutes to each assessment battery. We shortened the GoStop task by 2 minutes making a net change of 2-3 minutes. The ICF was modified to include the name of Peter Snyder, PhD who developed the GMLT as co-investigator of the study.

IRB Approved on 7/16/2007: Approval granted to offer subjects the opportunity to repeat the medication (or placebo) administration followed by the alcohol lab session in the event they missed a particular lab session after they have completed the entire set of 4 planned medication (placebo) administrations in order to make full use of the data from fully completed paired medication and alcohol lab sessions for that subject. In other words, an additional pre-lab visit and matching lab session will be offered to individuals who have completed 4 pre-lab visits and 3 matching lab visits (however, miss the 4th lab visit). The additional pre-lab visit and matching lab session will be identical to the visits that the subject missed due to unforeseen events (ie drug or placebo and alcohol or placebo drink). These visits will take place approximately one month after the subject finishes their scheduled series of study visits. The subject will be asked to sign an additional consent form explaining these procedures & any risks. The study phone script was modified to clarify and further explain certain details concerning the subject's involvement in the study. A statement concerning duration of study visits and method of blood draws, at each lab session, through an IV catheter in the arm, has been added to the phone script. The study quick reference criteria list for staff use was modified to add information concerning the amount of blood that will be drawn at each of the visits, and it's method through an IV catheter. Questions #15a, 30, and 39-43 were added to the study phone screener and questions #20, 21, 21a, 21b, 26b, 30b, and 34 were modified to assist with the careful screening of subjects for study eligibility.

IRB Approved on 10/18/2007: Approval granted to offer pre-screening brief visits, particularly for interested UConn Storrs campus students or staff which would occur at the Storrs campus (Psychology Department interview room) to avoid participants who screen out based on Body Mass Index (BMI), medical history or genetic inclusion criteria from needing to travel to UCHC. We also offer this brief pre-screening visit at the UCHC clinical site for subjects who live nearby and would not be inconvenienced to attend both a pre-screening visit and a baseline study screening visit should they meet study inclusion criteria at the pre-screening visit. Approval granted for an additional ICF, ICF Form C, and Medical History form for the pre-screening visit. Details of the pre-screening visit were added to the study phone script and study criteria list. Approval granted to include the following forms as part of a nursing history packet (in addition to the previously IRB approved nursing history): Physician's Order Sheet, Nursing Medical Administration Record, Medical and Alcohol Administration Sheet, EZ Screen, Physician's Sober exam, Progress Notes, Physical Exam report, Medical Review of Systems, and Psychiatric Review of Systems. Approval granted to have subject #619-006 repeat this lab session after his fourth lab session. In the contingency response letter of this review, a typographical error was addressed to the approval of a repeat lab session for subject #619-006. The correct subject for the repeated lab session was subject #619-004. Please note that the IRB approval letter was not modified to reflect the correction made of subject #619-006 to subject #619-004.

IRB Approved on 11/9/07: Dr. Carolyn Drazinic was IRB approved as a co-investigator for this study to provide additional MD cross-coverage if needed. ICF and protocol version dates were revised.

IRB approved at time of annual renewal January 2008:

We requested the removal of Amira Pierucci-Lagha, PhD as co-investigator for she is no longer employed at the UCHC nor affiliated with this study. Please note that removal of Dr. Pierucci-Lagha was submitted on the 3/7/2007 IRB approved continuation. However, her name still appears on all IRB approval cover letters & notices. We have modified the HIPAA Authorization form, used for the pre-screening visit and screening visit, with the updated version/language now required by the IRB. A recruitment web site URL - [www.uchcalcoholstudy.com](http://www.uchcalcoholstudy.com) (refer to study #2) - was added to all recruitment materials for this study. The PI purchased a short easy to remember URL [www.uchcalcoholstudy.com](http://www.uchcalcoholstudy.com) for a site that we may use to link interested potential participants to our study brochure, ICF and contact information contained in a separate web page. Currently, subjects are providing timeline follow-back data on their alcohol and drug consumption. IRB approval given to contact subjects one month after completion of their last visit (4th lab visit, or IRB approved repeat visit) to gather alcohol consumption data for the 30 days that follow the last visit. On the day of the fourth laboratory visit, subjects will be given a pre-paid stamped envelope and a timeline follow-back calendar, for the 30 days that follow the last visit. Subjects will be asked to complete the timeline follow-back calendar with the number of alcohol beverages consumed within the past 30 days, and mail it back to the study staff at UCHC. Subjects will be given a reminder call when the 30 days are soon to be due. If a subject fail to mail the timeline follow-back data after the 30 days, study staff will contact the subject to potentially collect the data over the phone. This information has been added to the study protocol and ICF. This final 30-day reporting of alcohol use will provide additional information to monitor whether study

participation including the pre-lab medication influences alcohol use outside of the study visit and to allow comparison of the 4 lab study conditions on such alcohol use. Addressed IRB guidelines for deoxyribonucleic acid (DNA) testing in protocol: The study protocol and ICF were modified to address the DNA/genetic testing aspects of this research study as recently requested by the IRB. The following elements have been fully addressed in the protocol: An explanation of the purpose of the DNA testing aspects of this research study and a description of the DNA test to be run on the collected samples. A description of any foreseeable risks and discomforts to the subjects regarding DNA testing. A description of any benefits to the subject or others that may reasonably be expected from the Deoxyribonucleic Acid (DNA) testing. A statement describing the extent, if any, to which the confidentiality of these records/samples identifying the subject will be maintained. To responds to new IRB guidelines regarding DNA sample storage: The protocol and ICF have also been modified to explain that all DNA samples and data sets will be completely de-identified at the conclusion of subject enrollment and completion of the primary outcomes analysis. A notification will be sent to the IRB once all DNA samples and phenotypic data are completely de-identified. The protocol was updated to provide information concerning the use of a Certificate of Confidentiality (CC) from the Food and Drug Administration (FDA) under the Section 301(d) of the Public Health Service Act (42 U.S.C. 241 (d)) to protect the researchers from being forced, even by court order or subpoena, to identify research subjects. (Please note that the CC was IRB approved on 4/12/2007). All ICF's were modified to include "DAIc" as an abbreviation to the studies name. This will help study staff distinguish and identify the informed consents for this study.

6) Continued GCRC support requested - We request the GCRC protocol remain active, resource needs - GCRC clinic exam room for alcohol lab sessions, GCRC nursing/research assistant support for alcohol lab sessions, ancillaries, core lab for hormone assays, DNA isolation and genotyping.





genotyping of the study sample for pharmacogenetic purposes.

**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
<b>START DATE:</b>	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	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
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SULLIVAN, TAMI 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:

During this reporting period the study protocol was developed and programmed into the Interactive Voice Response (IVR) system. Three participants pilot tested the protocol. Full implementation of the study began in December. Sixteen participants have been enrolled in the study and 1 participant completed the study. The response rate for the IVR group (one of the three groups in the study and the only group that has a connection to the GCRC) was 52.00%. No publications have been written about this study.

<b>SPID:</b>	0623	<b>PROTOCOL:</b>	623	<b>TYPE:</b>	RESEARCH	
<b>SHORT TITLE:</b>	Contingency Management					
<b>LONG TITLE:</b>	Contingency Management for Substance Abuse Treatment					
<b>AIDS:</b>	N	<b>TOTALS</b>		<b>A</b>	<b>B</b>	<b>D</b>
		Inpatient		0	0	0
<b>START DATE:</b>	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		1,125	0	0
<b>RESEARCH BIONUTRITION</b>	N	<b>MULTICENTER STUDY</b>		N		
<b>INFORMATICS CORE</b>	Y	<b>CLINICAL TRIAL</b>		N		
<b>BIOSTATISTICIAN</b>	N	<b>CORE LAB</b>		N		
<b>ANCILLARIES ONLY</b>	N					

<b>INVESTIGATOR</b>	<b>DEPARTMENT</b>	<b>NON-HOST INSTITUTION: STATE, COUNTRY</b>
PETRY, NANCY PHD	Psychiatry	
ALESSI, SHEILA PHD	Psychiatry	

#### 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: 271

Past Year Enrollment: 79

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 Justyna Tymoszczuk and Shanelle Carmichael as consenters, Jeremiah Weinstock as study coordinator and Ellen Ciesielski as study contact. 2) Revised study screening form to include a space for the research assistant to initial this form. 3) Partial Consent Waiver to complete screening approved. 4) Added the Methadone Treatment History Questionnaire. 5) Changed the timeframe in which study enrollment occurs from 48 hours to 1 week after treatment start for those being recruited from outpatient programs in order to facilitate recruitment. 6) Deleted a phrase in the Inclusion Criteria section of the protocol that refers to a recruitment site was approved to be removed from the protocol on 9/18/06. 7) Revised screener form to facilitate study recruitment. The additional questions help to better determine preliminary eligibility based on basic inclusion/exclusion criteria. 8) Added Dr. Jeremiah Weinstock as member of the DSM Committee for this study. 9) Three questions added to the Addiction Severity Index regarding Medical Status and Drug/Alcohol Use. 10) A comments Box is added to the bottom of page 2 of the Brief Symptom Inventory to document any discussion regarding suicidal or homicidal ideation if needed for potential adverse events records. 11) Additional codes and spaces were added to the Service Utilization in order to improve the accuracy of data collection and questions regarding visits with parole officers were also added. 12) Clarified that a modified version of the SCID is used to measure antisocial personality disorder. 13) Removed Marcia DeSousa and added Trisha Feery as a consenter. 14) Added questions to the Addiction Severity Index (ASI) regarding HIV status and previous and current treatment. 15) Revised Cigarette Smoking History questionnaire.
- Results not yet published as study is ongoing.

Do you wish to continue to receive GCRC resources for the period April 1, 2008 through March 31, 2009? Yes

**SPID:** 0624      **PROTOCOL:** 624      **TYPE:** RESEARCH

**SHORT TITLE:** Omega-3  
**LONG TITLE:** Effects of Omega-3 Fatty Acids on Bone and Fragility

AIDS:	N	<b>TOTALS</b>	<u>A</u>	<u>B</u>	<u>D</u>
			Inpatient	0	0
<b>START DATE:</b>	4/20/2006	Scatter Bed	0	0	0
Total # pts expected for entire study:	150	Outpatient	302	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		

<b>INVESTIGATOR</b>	<b>DEPARTMENT</b>	<b>NON-HOST INSTITUTION: STATE, COUNTRY</b>
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KENNY, ANNE MD	Center on Aging	
LAMMI, KEEFE PHD	NUTRITION	UConn, Storrs, CT USA
PILBEAM, CAROL MD, PHD	Medicine	
SECOR, ERIC MD	Immunology	
THRALL, ROGER 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 recruited 125 subjects, shy of the 150 we had hoped to recruit due to slow recruitment in the beginning. We modified the inclusion criteria and resulted in markedly improved recruitment. We have had very few drop outs (only 7) and all have been for minor complaints. No unexpected safety concerns have been noted. There are no interim outcomes available at this time. No publications have occurred. The last subject will complete the study in the end of July and data analysis will begin at that time.

**SPID:** 0625      **PROTOCOL:** 625      **TYPE:** RESEARCH

**SHORT TITLE:** Androgen Receptor  
**LONG TITLE:** Androgen Receptor Polymorphisms in East Asian Men

	AIDS:	N	<b>TOTALS</b>	<b>TOTALS</b>		
				A	B	D
			Inpatient	0	0	0
<b>START DATE:</b>		5/18/2006	Scatter Bed	0	0	0
Total # pts expected for entire study:		0	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	Y
ANCILLARIES ONLY	N		

<b>INVESTIGATOR</b>	<b>DEPARTMENT</b>	<b>NON-HOST INSTITUTION: STATE, COUNTRY</b>
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RAJAN, THIRUCHANDURAI V MD, PHD	Pathology	
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**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:**

During the reporting period in question we were provided the following services from the GCRC: Sample collection, Deoxyribonucleic Acid (DNA) extraction, and genotyping on androgen receptor polymorphisms.

This study closed to enrollment in July of 2007 and is currently in data analysis. We hope to have publications based on this data published within the next year.

<b>SPID:</b>	0626	<b>PROTOCOL:</b>	626	<b>TYPE:</b>	RESEARCH	
<b>SHORT TITLE:</b>	Asthma					
<b>LONG TITLE:</b>	Genes, Home Allergens and Asthma in Puerto Rican Children					
<b>AIDS:</b>	N	<b>TOTALS</b>		<b>A</b>	<b>B</b>	<b>D</b>
		Inpatient		0	0	0
<b>START DATE:</b>	5/18/2006	Scatter Bed		0	0	0
Total # pts expected for entire study:	100	Outpatient		158	0	0
		Scatter RN Hours		0	0	0
		Offsite Visits		239	0	0
RESEARCH BIONUTRITION	N	MULTICENTER STUDY		N		
INFORMATICS CORE	Y	CLINICAL TRIAL		N		
BIOSTATISTICIAN	N	CORE LAB		N		
ANCILLARIES ONLY	N					

<b>INVESTIGATOR</b>	<b>DEPARTMENT</b>	<b>NON-HOST INSTITUTION: STATE, COUNTRY</b>
CLOUTIER, MICHELLE MD	Pediatrics	

#### SUBPROJECT DESCRIPTION:

Asthma affects over 14 million people in the United States.<sup>1</sup> 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,<sup>18</sup> 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.<sup>19</sup> In these children, we have shown that Puerto Rican ethnicity is associated with sensitization to specific allergens and increased asthma severity.<sup>20, 21</sup> 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).<sup>22</sup> In atopic children, production of cytokines (IL-4, IL-5, IL-9, and IL-13) by T-helper (Th)<sub>2</sub> cells promotes increased production of immunoglobulin E (IgE), eosinophilia, mast cell differentiation, and long-term expression of allergen-specific immunity.<sup>23,24</sup> Atopy and atopic asthma may result from lack of upregulation of Th<sub>1</sub> immune responses and/or inadequate downregulation of Th<sub>2</sub> immune responses.<sup>25, 26</sup> We hypothesize that single nucleotide polymorphisms (SNPs) in genes that control the development and regulation of Th<sub>1</sub> cells, Th<sub>2</sub> 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 FEV<sub>1</sub> and FEV<sub>1</sub>/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 Th<sub>1</sub> cells, Th<sub>2</sub> 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, FEV<sub>1</sub>, FEV<sub>1</sub>/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 4/01/07-3/31/08 we enrolled a total of 227 children into our genetic study. In total, to date, we have enrolled 421 children. We continue to make good progress on this project. On average, our no show rate for the home visits is ~43% while the no show rate for the hospital visits is ~38%. While these rates are significant, they are anticipated. In an effort to address attendance to the home and hospital visits, we continue to place reminder calls to the families the day before the scheduled visit as well as on the day of the visit. In addition, we also mail reminder letters that include magnets with the family's appointment information and our office phone number.

Recruitment efforts continue to focus within Hartford public schools during the academic year (flyer distribution, attendance at Open House, parent/teacher conferences, PTO meetings, and after school programs). When weather permits, we also conduct live recruitment after school when parents typically go to the school to pick their child up. In addition, throughout the school year, we make efforts to attend various health fairs in Hartford. As summer vacation approaches, we will be focusing our recruitment efforts at the Boys and Girls Clubs in Hartford as well as other community agencies (i.e. Mi Casa, Hispanic Health Council, summer camps, etc.).

To date, we have not experienced any unexpected safety issues while conducting recruitment or study visits and we do not anticipate any safety concerns. However, study equipment was stolen from our office in January 2008 (one laptop and one KoKo spirometer). Appropriate individuals were notified and replacement equipment was secured via Connecticut Children's Medical Center (CCMC). Various CCMC IRB approved safety precautions have been identified and implemented; these were outlined and approved by the CCMC IRB.

We continue to collaborate with our colleagues in Boston. No publications have resulted from this work to date, as it is too early. Based on recent scientific evidence that vitamin D may influence the pathogenesis of asthma and asthma morbidity, our Boston colleagues propose that we measure vitamin D levels in blood samples. Due to the impracticality of re-consenting existing participants (addresses and phone numbers frequently change), we wish to do this by using the blood samples that we have already collected on existing participants. We submitted a request to the CCMC IRB on 4/18/08, the IRB of record, requesting permission to modify our consent form to indicate that blood collection will be used to measure vitamin D levels in addition to gene testing (DNA) and allergy testing. We are awaiting approval.

<b>SPID:</b> 0628	<b>PROTOCOL:</b> 628	<b>TYPE:</b> 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
<b>START DATE:</b>	5/30/2006	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	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, retention, 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 4/1/2007 until 3/31/2008, 6 women enrolled. Since the initiation of this pilot study, 9 woman enrolled and all have completed the study. Modifications to the project approved by the Institutional Review Board (IRB) this year include: 1) Approval of the Informed Consent Form (ICF) and Protocol revisions to reflect new IRB rules and language regarding storing of samples. Samples will no longer be stored beyond completion of the study. 2) Approval the removal of Dr. Madhavi Mallareddy as a co-investigator. Dr. Mallareddy has completed her fellowship and is not longer affiliated with UCHC. Dr. White has assumed her responsibilities. 3) Approval of revised HIPAA; language changed to comply with new IRB guidelines dated 9/2007. 4) A Principal Investigator (PI) back up form was approved naming study coordinator Dr. Gina Abbott as PI Back up.

There are no unexpected safety concerns.

Preliminary data shows support for the hypotheses, and feasibility of conducting this multi-faceted study. PI is submitting a larger grant (R01) based on this pilot data.

There are no publications at this time.

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**SPID:** 0629      **PROTOCOL:** 629      **TYPE:** RESEARCH

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**SHORT TITLE:** ATOM  
**LONG TITLE:** Contingency Management Reinforcement for Adolescent Cannabis Abuse

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AIDS:	N	TOTALS	A	B	D
		Inpatient	0	0	0
<b>START DATE:</b>	6/15/2006	Scatter Bed	0	0	0
Total # pts expected for entire study:	72	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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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 is 22 and since initiation of the study is 59. The study is now closed to enrollment; therefore 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

**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	<b>TOTALS</b>	A	B	D
			Inpatient	0	0
<b>START DATE:</b>	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 MD	Psychiatry	
SCOTT, DENISE BS	GENETICS	HOWARD UNIVERSITY, DC USA
TAYLOR, ROBERT 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  $\alpha$ -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:

- 1) Number of subjects enrolled during the report period: none; since initiation of study: 149
- 2) Planned changes in recruitment plans: Preliminary results from this and from GCRC#560 were used in support of a new grant application which was recently funded to continue this project by enrolling a larger sample of Howard University college students (approximately 150 students each semester for 6 semesters).
- 3) Unexpected safety concerns and their resolution: None occurred.
- 4) Interim data: Salivary Deoxyribonucleic Acid (DNA) has been prepared from the 149 participants to date and used to generate genotype data at the 5HTTLPR locus and the HTR1B 3'UTR polymorphism. The sample is too at this time for genetic

association studies of behavioral phenotypes.

5) Proposed changes made or anticipated in the protocol: The new R21 grant supporting subject recruitment at Howard University includes specific aims to examine awakening salivary cortisol as a potential biological marker of recent stress or stress reactivity. GCRC core lab assay of salivary cortisol from 4 samples collected on 4 occasions from each participant has been added to the GCRC protocol. Interactive Voice Response (IVR) will be used to track subject compliance with collection parameters for awakening salivary cortisol.

6) Continued GCRC support requested - core lab for salivary DNA, genotyping and salivary cortisol. Informatics support for IVR.

<b>SPID:</b> 0632	<b>PROTOCOL:</b> 632	<b>TYPE:</b> RESEARCH
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<b>SHORT TITLE:</b>	Racism in Minority Children
<b>LONG TITLE:</b>	Perceptions of Racism in Minority Children

	AIDS:	N	TOTALS	A	B	D
			Inpatient	0	0	0
<b>START DATE:</b>	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	21	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 MD	PEDIATRICS	INSTITUTE OF LIVING, 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 finished enrollment and enrolled 35 new participants into the study. This raises our final total subject number to 277. We have begun data analysis during this report period as well. We are in the process of using the data to develop and refine an instrument to measure perception of racism in children and youth, using traditional psychometric analyses as well as structural equation modeling. We have also begun descriptive analyses of the occurrence of perceptions of racism in this sample, vis-à-vis race/ethnicity, age, and gender. We are in the process of writing manuscripts for publication.

**SPID:** 0634      **PROTOCOL:** 634      **TYPE:** RESEARCH

**SHORT TITLE:** Serotonin 1A  
**LONG TITLE:** Serotonin 1A Receptor and Mood in Daily Life

AIDS:	N	TOTALS	A	B	D
		Inpatient	0	0	0
<b>START DATE:</b>	5/30/2006	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	N
ANCILLARIES ONLY	N		

INVESTIGATOR	DEPARTMENT	NON-HOST INSTITUTION: STATE, COUNTRY
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CONNER, TAMLIN PHD	Psychiatry	
COVAULT, JONATHAN MD, PHD	Psychiatry	
KRANZLER, HENRY 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 (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 and examining single gene associations with daily emotional outcomes. No additional subjects have enrolled since the start of this project on April 1, 2006 or since the previous GCRC progress report. No changes in recruitment plans were needed and no unexpected safety concerns have arisen. All genotyping and costs associated with the project was completed in 2007.

The primary hypotheses relating to the HTR1A polymorphism to daily mood states were unsupported (reported in 2007 Progress Report); therefore, remaining funds were used to genotype SNPs in the tryptophan hydroxylase-2 (TPH2) gene [G(-703)T SNP (rs4570625) and the T(-473)A SNP (rs11178997)], CRHR1 (rs1876831), and DRD4 (VNTR polymorphism in exon III). Furthermore, analyses were expanded to examine associations between these SNPs and daily alcohol use.

#### FINAL OUTCOMES

1. Analyses of associations between TPH2 SNPs and alcohol use have resulted in publication (Gacek, Conner, Tennen, Kranzler, & Covault, in press). Findings replicated prior research showing no association between the TPH2 rs4570625 SNP and quantity and frequency of alcohol use in this non-clinical population. The GCRC is cited in the acknowledgement section

of the paper. A final copy of the paper will be sent to the GCRC when it is published.

Gacek, P.\*, Conner, T. S., Tennen, H., Kranzler, H. & Covault, J., (in press).

Tryptophan Hydroxylase 2 Gene and the alcohol use among college students.

Addiction Biology

\*UHC Master's in Public Health student Paul Gacek

2. Analyses of associations between TPH2 snps and daily mood states showed

significant results. 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. These patterns were three times as strong as associations found with traditional retrospective survey measures. Results will be written up for publication.

3. Statistical analyses of the CRHR1 and DRD4 snp data will be conducted over the 2008-2009 academic year. Results will be used for publications and to inform decisions whether similar genotyping should be done in a larger genetic data set currently being collected at UHC (P.I., Howard Tennen).



**SPID:** 0635      **PROTOCOL:** 635      **TYPE:** RESEARCH

**SHORT TITLE:** Hip Fracture Pilot  
**LONG TITLE:** Feasibility of Multi-Component Training in Patients 2 Months Post Hip Fracture

AIDS:	N	TOTALS	A	B	D
		Inpatient	0	0	0
<b>START DATE:</b>	5/30/2006	Scatter Bed	0	0	0
Total # pts expected for entire study:	8	Outpatient	6	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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KENNY, ANNE MD	Center on Aging	
FORTINSKY, RICHARD BA	Center on Aging	

#### SUBPROJECT DESCRIPTION:

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.

#### SUBPROJECT PROGRESS:

The study has received Institutional Review Board (IRB) approval. We are working with orthopedic surgeons and local home care agencies to identify potential participants. We have recruited 3 subjects into the study and have 2 more in the screening process. We continue to work with orthopedic surgeons to identify subjects. We have had no safety concerns but one subject did fall and sustain a broken pelvis (during usual activities, not during the intervention). No manuscripts have been prepared from the data yet.

<b>SPID:</b>	0636	<b>PROTOCOL:</b>	636	<b>TYPE:</b>	RESEARCH	
<b>SHORT TITLE:</b>	Marital Interaction					
<b>LONG TITLE:</b>	Marital Interaction in Alcoholic Couples Over Time					
<b>AIDS:</b>	N	<b>TOTALS</b>		<b>A</b>	<b>B</b>	<b>D</b>
		Inpatient		0	0	0
<b>START DATE:</b>	7/20/2006	Scatter Bed		0	0	0
Total # pts expected for entire study:	100	Outpatient		38	0	0
		Scatter RN Hours		0	0	0
		Offsite Visits		0	0	0
<b>RESEARCH BIONUTRITION</b>	N	<b>MULTICENTER STUDY</b>		N		
<b>INFORMATICS CORE</b>	Y	<b>CLINICAL TRIAL</b>		N		
<b>BIostatistician</b>	N	<b>CORE LAB</b>		N		
<b>ANCILLARIES ONLY</b>	N					

<b>INVESTIGATOR</b>	<b>DEPARTMENT</b>	<b>NON-HOST INSTITUTION: STATE, COUNTRY</b>
CRANFORD, JAMES 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:**

UCHC GCRC Progress Report Summary for Project 5R21 AA015105-02. The targeted enrollment for this project was n=50 alcoholic couples. In our previous progress report, we indicated that n=5 couples had completed the Time 1 (T1) interview and marital interaction task. We also indicated that we had submitted a request for a second set of modifications to the research protocol to the UCHC IRB on 04.13.07. These modifications, which included expansion of recruitment efforts, revisions to the informed consent, and changes to the recruitment brochure, were approved by the University of Michigan (U of M) Medical School IRB on 03.22.07 (Amendment eResearch ID: Ame00003772) and by the UCHC IRB on 05.21.07 (UCHC IRB Number: 07-035-3). Unfortunately, this expansion of recruitment efforts was not sufficient for us to meet our recruitment goals, and we therefore submitted a request for a third set of modifications to the research protocol. These modifications involved further expansion of recruitment efforts to include 1) unmarried heterosexual couples (18 or older) who have been living together in a committed relationship for at least 6 months; 2) posting the study on the University of Michigan Clinical Outcomes and Research Engine (M-Strides) and on public websites (e.g. Craig's list, Arborlist, etc.); and 3) distributing recruitment brochures to local bars and churches in the Ann Arbor area. This third request was approved by the U of M IRB on 09.05.07 (Amendment eResearch ID: Ame00005000), and by the UCHC IRB on 10.11.07 (UCHC IRB Number: 07-035-3). In addition, the first Scheduled Continuing Review (SCR) of this project was approved by the U of M Medical School IRB on 04.28.07 (SCR eResearch ID: CR00003882) and by the UCHC IRB on 09.10.07. The second SCR of this project was approved by the U of M Medical School IRB on 03.07.08 (SCR eResearch ID: CR00006849 <<https://eresearch.umich.edu/eresearch?PageID=CR00006849>>).

Expansion of recruitment efforts allowed us to exceed our targeted enrollment, and we were able to recruit n=54 alcoholic couples into this study. Recruitment was closed on 01.15.08, and the final couple completed their T1 interview on 02.09.08. This final couple completed their final call to the UCHC Interactive Voice Response (IVR) system on 03.11.08. Given that our final sample size was N=54 couples, with each spouse asked to complete 14 daily reports on their drinking, marital interactions, and moods every night for 14 consecutive nights using the UCHC IVR system, our IVR data set had a maximum of  $54 \times 2 \times 14 = 1,512$  observations or diary days. Participants in our study completed a total of 1,418 IVR reports. Thus, our total compliance rate was  $1,418 / 1,512 = 93.8\%$ .

Couples are also asked to complete telephone interviews at T2 (6 months after T1) and T3 (12 months after T1). As of today (05.11.08), n=23 couples have completed the T2 interview and n=5 couples have complete the T3 interview. Due to recruitment challenges, data collection will continue beyond the originally scheduled end date of May 31st, 2008. Accordingly, we submitted a request for a 12-month No-Cost Extension (NCE) to NIH on 03.13.08. This request was approved by NIH on 03.31.08, and the new end date for this project is now 05.31.09. No unexpected safety concerns have arisen and no further changes to the protocol are anticipated. Because the final IVR data were collected only 2 months ago, we have not yet published any results from this project. However, an abstract based on this project was recently accepted by the Research Society on Alcoholism. As indicated below, this abstract cites the U of M and UCHC GCRCs.



**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
<b>START DATE:</b>	7/18/2006	Scatter Bed	0	0	0
Total # pts expected for entire study:	96	Outpatient	17	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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HESELBROCK, VICTOR PHD	Psychiatry	
GRAVELEY, BRENTON PHD	Genetics and Developmental	
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:

DNA methylation, which is thought to play an important role in carcinogenesis, is an emerging area of epigenetic research. Consistent with NIH Roadmap initiatives, a multidisciplinary investigative group from UCHC responded (Drs. Bonkovsky, Hesselbrock, Lalande, and Lambrecht) is examining the 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. To achieve these aims we proposed 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<sup>17</sup> 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,<sup>1</sup> 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 were drawn from the COGA study sample. After being consented, 15 mL of peripheral blood was obtained and peripheral blood monocytes (PBM) was separated for DNA extraction using the Progene DNA purification kit and the standard protocol currently in use at the GCRC Core Lab. The plasma is being stored frozen (-80oC) in 1 mL aliquots for possible future use. The DNA samples, stored at -80oC were processed by the Molecular Core Lab under the supervision of Dr. B. Graveley. The DNA methylation pattern has been studied using the methylation chip from Illumina labs. We are continuing to analyze the results for differences in the methylation patterns in the sibling pairs. GCRC resources have been used for recruitment and enrollment of subjects (Clinical 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 was considerably slower than expected. To date only 29 sibling pairs, from a total of n=55 subjects, were recruited and have also provided blood samples for DNA extraction. Following completion of this last subject pair, DNA extraction was completed on all samples and the DNA sent to Dr Gravely's lab to examine the DNA methylation pattern using the recently available methylation chip obtained from Illumina labs.

An initial analysis of these pilot data revealed no clear methylation pattern attributable to chronic alcohol use, but more careful analysis using other alcohol-related phenotypes -apart from a formal diagnosis - is underway. There have been no unexpected safety concerns from this study; no publications or presentations have resulted from this work to date.

**SPID:** 0638      **PROTOCOL:** 638      **TYPE:** RESEARCH

**SHORT TITLE:** Osteoporosis and Bone Augmentation

**LONG TITLE:** Osteoporosis and Bone Augmentation/Implant Outcomes: An Observational Study

	AIDS:	N	<b>TOTALS</b>	<b>TOTALS</b>		
				<b>A</b>	<b>B</b>	<b>D</b>
			Inpatient	0	0	0
<b>START DATE:</b>		9/21/2006	Scatter Bed	0	0	0
Total # pts expected for entire study:		120	Outpatient	75	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		

<b>INVESTIGATOR</b>	<b>DEPARTMENT</b>	<b>NON-HOST INSTITUTION: STATE, COUNTRY</b>
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FREILICH, MARTIN A DDS	Prosthodontics	
PENDRYS, DAVID DDS, PHD	Behavioral Sci & Comm Hlth	

#### **SUBPROJECT DESCRIPTION:**

Bone augmentation is frequently a necessary component of dental implant reconstruction. While in the future, tissue engineering methods including cell transplantation and the release of cell signaling agents will be available for clinical use, the current gold standard to increase bone volume is through autogenous grafting. Grafting tends to be successful in young healthy patients, but there is evidence that success rates of grafting procedures markedly decrease with age and certain systemic conditions, such as osteoporosis. In the US, there are roughly 10 million women over the age of 50 with osteoporosis and an additional 34 million with low bone mass or osteopenia." It is estimated that 40-50% of women over the age of 50 will sustain an osteoporotic fracture in their remaining lifetime. Given that a statistically significant correlation has been shown between hip and mandible BMD, this large population may be at increased risk for complications and low success rates for bone augmentation procedures compared to women with healthy bone. The relationship between this systemic health problem and implant success is not well documented and additional research in this area is needed. Despite the suggestion of the negative effect of low bone density/osteoporosis to bone graft success, no studies have been reported which carefully demonstrate this relationship.

#### **SUBPROJECT PROGRESS:**

Forty-two patients have signed consent at a screening visit and of those, 11 cases screen failed, 7 cases need to be reviewed to determine eligibility for the second of screening visits/Treatment planning visit, 24 have passed onto the second screening/Treatment plan visit. Of those 24 cases, 2 withdrew, 4 have failed out, 4 cases need to be reviewed, 4 are pending surgery and 10 have been baselined (i.e. received implants).

Changes in recruitment plans during the above-mentioned time period have included adding posters, brochures, and opening the recruitment to the general public. No major scientific changes have been made to the protocol since the studies inception. However addendums included the addition of a surgical consult appointment prior to bone augmentation/implant surgery appointment in which the provider reviews the treatment plan with the patient and obtain standard consent for surgery. The following changes were made to the inclusion and exclusion criteria are being made. Inclusion of those requiring a sinus elevation procedure less than or equal to 2mm in combination with their dental implant placement was also added to the protocol.

No interim data or outcomes are available at this time. No publications have been produced as a result of this study as of yet.

<b>SPID:</b> 0639	<b>PROTOCOL:</b> 639	<b>TYPE:</b> 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
<b>START DATE:</b> 9/21/2006		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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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 CO<sub>2</sub> 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 CO<sub>2</sub>.

#### SUBPROJECT PROGRESS:

This study was approved by the General Clinical Research Center (GCRC) for 6 subjects which were enrolled. A manuscript is in preparation.



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**SPID:** 0640      **PROTOCOL:** 640      **TYPE:** RESEARCH
 

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**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
<b>START DATE:</b>	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	N	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:**

Adam Lubinguhl graduated from Uconn School of Medicine in May 2007 and is now an Otolaryngology resident in Philadelphia. There has been no additional subject enrollment since the prior progress report. Follow-up was updated late in 2007 during preparation of an abstract for submission to the upcoming (July 2008) International Conference on Head and Neck Cancer. The study was accepted for a podium (oral) presentation at this upcoming meeting, and we plan on submitting a manuscript for publication as well. The GCRC will be cited in both cases.

<b>SPID:</b> 0641	<b>PROTOCOL:</b> 641	<b>TYPE:</b> RESEARCH
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<b>SHORT TITLE:</b>	Stressors
<b>LONG TITLE:</b>	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
<b>START DATE:</b>	12/21/2006	Scatter Bed	0	0	0
Total # pts expected for entire study:	100	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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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:

Number of subjects enrolling (Correction to last year's stats)

Time Frame	Enrolled	Screened
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4/1/06-3/31/07	7	16
4/1/07-3/31/08	30	53
4/1/08-6/09/08	4	7

30 patients have been enrolled and 53 screened for the progress report period. There are no changes to recruitment plans. We plan to continue until we meet the recruitment goal of 100 patients. There are no unexpected safety concerns. Interim data was presented October 2007 to the Board of Directors of the CT Breast Health Initiative, Inc. (Please see attached slide). Jayesh Kamath is presenting an abstract at the IPOS 10th World Congress of Psycho-Oncology in Madrid, Spain (Please see attached PDF). There have been no changes made to the protocol within the reporting period. The slide presentation does include reference to the GCRC.

<b>SPID:</b> 0642	<b>PROTOCOL:</b> 642	<b>TYPE:</b> 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	<b>TOTALS</b>	A	B	D
			Inpatient	0	0
<b>START DATE:</b>	11/16/2006	Scatter Bed	0	0	0
Total # pts expected for entire study:	1	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 II
BIostatistician	N	CORE LAB	N	
ANCILLARIES ONLY	N			

<b>INVESTIGATOR</b>	<b>DEPARTMENT</b>	<b>NON-HOST INSTITUTION: STATE, COUNTRY</b>
SALAZAR, JUAN MD	Pediatrics	

#### 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 II 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 subject participating at the Connecticut Children's Medical Center site since the opening of the study. Due to non-refunding of our site, this subject was discontinued from study participation as of Nov 2007.

This study has been closed to accrual.

There have been no unexpected safety concerns reported by The PACTG 1047 team.

<b>SPID:</b>	0643	<b>PROTOCOL:</b>	643	<b>TYPE:</b>	RESEARCH	
<b>SHORT TITLE:</b>	HITEC					
<b>LONG TITLE:</b>	Health Improvement Through Training and Employee Control (HITEC)					
<b>AIDS:</b>	N	<b>TOTALS</b>		<b>A</b>	<b>B</b>	<b>D</b>
		Inpatient		0	0	0
<b>START DATE:</b>	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
<b>RESEARCH BIONUTRITION</b>	N	<b>MULTICENTER STUDY</b>		N		
<b>INFORMATICS CORE</b>	Y	<b>CLINICAL TRIAL</b>		N		
<b>BIostatistician</b>	N	<b>CORE LAB</b>		N		
<b>ANCILLARIES ONLY</b>	N					

<b>INVESTIGATOR</b>	<b>DEPARTMENT</b>	<b>NON-HOST INSTITUTION: STATE, COUNTRY</b>
CHERNIACK, MARTIN MD	Occupational/Environmental	

#### 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:

Subjects: There are no subjects currently enrolled in this project.

Personnel: There were no changes in key personnel over the year. Professor Vicki Magley in the Department of Psychology at UCONN-Storrs has formally joined the project as an investigator. Her background is in workplace violence. Her involvement and the incorporation of HITEC and CPH-NEW fieldwork with the NIOSH-funded industrial psychology program at UCONN, has brought 3 new graduate trainees into HITEC. Currently, 7 graduate students from UCONN Health Center and UCONN-Storrs are engaged in the project as their field practicum or as part of their thesis work.

AIMS: HITEC has selected 2 matched sites, facilities with the State of Connecticut Department of Corrections. These currently active study sites represent a departure from the original plan to use only Travelers clients, but reflected the strong interest on the part of the State of Connecticut in the challenged health of corrections officers. Selection of the second pair of sites has not been concluded, and is discussed under Site Selection. The original Aims are presented below. 1. Creation of semi-independent employee sponsored participant (ESP) groups that will devise a program combining individual health promotion with a corresponding worksite health and safety intervention. 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). 3. Development of economic and econometric models for assessing effectiveness, costs, and benefits of interventions, and providing a program evaluation model that is understandable, reproducible, and acceptable to all participating parties, and in particular to insurers and financial representatives. 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. We have renamed the ESP sites participatory sites and refer to the SOC sites as professional sites. AIM #1 remains in process. Practically, we have prepared a series of operative scenarios based on participatory ergonomics to optimize the process. The evaluation process for site comparison (AIM #2) is in place and has not changed in principle since last year. Because of security considerations at DOC, environmental exposure evaluation has been modified. While the development of models (AIM #3) is an ongoing process, there has been considerable progress in compiling practical data bases. AIM #4 requires an adjustment. Because the State of Connecticut is self-insured, the model developed with Traveler's underwriters for pard assigning a cost threshold no longer applies. We have adjusted by working with the Comptrollers Office (group health) and the Department of Administrative Services (DAS) both to assure capital funding and to apply our cost-plus model to the public sector.

## Site Selection:

The DOC site selection process is described below. As noted in the Year I progress report, a sophisticated selection strategy involving 1200 Traveler's clients was unsuccessful. We have followed up on reasons for company caution with a survey to key personnel and to the responsible Traveler's account managers. Results have been presented (APA-NIOSH Work, Stress, and Health Conference, 3/7/08), and publication is in progress. The reasons for refusal are being studied with Traveler's to look for generalizable patterns.

We have continued to recruit through Travelers by holding Employer's Schools and have made solicitations outside of the Traveler's network. The following 13 companies and sites were screened and directly solicited with site visits, PowerPoint presentations and summaries of worker's compensation costs. The numbers conceal relatively different levels of recruitment effort. Sites 5 and 6 extended over 4 months each with preliminary agreements and site materials prepared. In both cases, the deteriorating economic climate and increased pressures from state regulators lead senior management to withdraw.

ID	Description	Traveler's Client	Location	No(*)	Yes	Pending	Status
1.	Accounting and finance	Yes	New York State	No			Poor financial climate
2.	Consumer warehousing	Yes	Mid-west	No*			Travel Costs
3.	Global manufacturing	No	CT and MA	No*			Restrictive policies
4.	Parts manufacturer	Yes	Northern mid-west	No*			Travel Costs
5.	Utility	No	CT	No			Poor financial climate
6.	Utility	No	CT and MA	No			Legal and financial client
7.	Precision manufacturer	Yes	CT	Pending			In review
8.	Drivers/DOT	No	CT	Pending			In review
9.	Insurer	Yes	CT and NY	Pending			In review
10.	Food manufacturer	Yes	CT and NY	No			Insurer conflict
11.	Warehouse work	No	MA and CT	No			Union contract issue
12.	Precision manufacturer	No	CT and NY	Pending			In review
13.	Aerospace manufacturer	No	CT	Pending			In review
14.	Electronics manufacturer	No	CT and MA	Pending			In review

(\*) HITEC rejected

The situation is far from negative. The Connecticut DOT (Site 8) and Travelers itself (Site 9) are very interested in participation but we have reserved them as defaults, because of an intent to diversify beyond two State agencies in the first case, and because of conflict of interest and low injury rates in the case of Travelers office workers. If the pending manufacturing sites decline over the next 2 months, we will engage either DOT or Travelers.

## Department of Corrections

The program at the Connecticut DOC is underway at two sites. There was an extensive selection process which involved clearances with all of the unions and the DOC administration. The MOU includes subsidization of time for participation in the study and an a priori commitment from the State for ergonomic related changes. The selection process involved four elements.

1. A review of worker's compensation, demographic, and facilities based records from all State facilities
2. Repeated site visits to 9 facilities, including meetings with key personnel
3. A management readiness survey was sent to 598 supervisors at 21 facilities, in order to identify most culturally similar organizations.
4. A DOC-wide steering committee was set-up involving central administration, wardens, union representatives and health personnel to advise on final selection, implementation and system-wide dissemination.

A summary of the two selected sites follows.



**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
<b>START DATE:</b>	11/16/2006	Scatter Bed	0	0	0
Total # pts expected for entire study:	25	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	Y
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:

The study has been actively screening women over the past year and we currently have enrolled 10 women during the above time frame. There is also 1 woman who is scheduled to start on 6/16/2008.

<b>SPID:</b>	0645	<b>PROTOCOL:</b>	645	<b>TYPE:</b>	RESEARCH	
<b>SHORT TITLE:</b>	SPOON					
<b>LONG TITLE:</b>	Impact of a Protein Supplement on Bone Mass in Older Women					
<b>AIDS:</b>	N	<b>TOTALS</b>		<u>A</u>	<u>B</u>	<u>D</u>
		Inpatient		0	0	0
<b>START DATE:</b>	12/21/2006	Scatter Bed		0	0	0
Total # pts expected for entire study:	230	Outpatient		200	0	0
		Scatter RN Hours		0	0	0
		Offsite Visits		2	0	0

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

<b>INVESTIGATOR</b>	<b>DEPARTMENT</b>	<b>NON-HOST INSTITUTION: STATE, COUNTRY</b>
KENNY, ANNE MD	Center on Aging	
ISOGNA, KARL MD	INTERNAL MEDICINE	YALE UNIVERSITY, CT USA
KERSTETTER, JANE PHD	NUTRITION	UCONN - STORRS, CT USA
WEIGERT, JEAN MD	RADIOLOGY	WOMEN'S IMAGING, CT USA

**SUBPROJECT DESCRIPTION:**

Because increasing dietary protein increases urine calcium and metabolic acid load and because systemic acidosis favors bone loss, it is thought that higher protein diets increase bone resorption and decrease Bone Mineral Density (BMD). However, most cross-sectional, population-based studies with bone density, or rates of bone loss as the principal outcome, indicate that higher dietary protein intakes are associated with higher (not lower) BMD and slower (not faster) rates of bone loss. Further, increasing dietary protein in subjects consuming low-normal protein diets increases circulating levels of IGF-1 which is known to be important for bone anabolism. Three recent diet-controlled isotopic calcium studies showed no net loss of calcium from bone during high protein diets in humans (1-3). In 1 of these 3 studies, we (1) showed that a high protein diet increased urinary calcium by increasing intestinal calcium absorption. Importantly, during the high protein diet, there was a significant reduction in the fraction of urinary calcium of bone origin and a trend toward a reduction in the rate of bone turnover. None of the 3 isotopic studies found evidence for increased bone loss with increasing dietary protein. In fact, they all suggest the opposite; higher protein diets actually improved calcium retention. These isotopic data lay the groundwork for a long-term protein intervention trial with BMD as the principal outcome variable.

**SUBPROJECT PROGRESS:**

The study is underway and recruitment is beginning. Approximately 47 women have been recruited into the study and 6 women have discontinued due to medical illness or not tolerating the inconvenience of taking the protein supplement. No unexpected safety concerns have arisen. We are considering changes to the inclusion criteria to improve recruitment efforts. There have been no publications from the study.

<b>SPID:</b> 0646	<b>PROTOCOL:</b> 646	<b>TYPE:</b> RESEARCH
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<b>SHORT TITLE:</b>	Gene Bank
<b>LONG TITLE:</b>	Behavioral Gene Bank

	AIDS:	N	<b>TOTALS</b>	<u>A</u> <u>B</u> <u>D</u>		
				Inpatient	0	0
<b>START DATE:</b>	12/21/2006		Scatter Bed	0	0	0
Total # pts expected for entire study:		500	Outpatient	16	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		

<b>INVESTIGATOR</b>	<b>DEPARTMENT</b>	<b>NON-HOST INSTITUTION: STATE, COUNTRY</b>
DRAZINIC, CAROLYN MD	Psychiatry	
COVAULT, JONATHAN MD, PHD	Psychiatry	
HESSELBROCK, VICTOR PHD	Psychiatry	
KRANZLER, HENRY MD	Psychiatry	
LALANDE, MARC MD	Genetics & Develop Biology	

**SUBPROJECT DESCRIPTION:**

The purpose of this registry/repository is collect diagnostic data (psychiatric and medical diagnoses) and tissue specimens from subjects and/or family members in order to build a Behavioral Gene Bank (BGB). The registry/repository aims to study: subjects with known or suspected genetic or medical syndromes; families with high concentrations of psychiatric illnesses; and subjects with dysmorphic features or other clinical characteristics suggestive of a genetic or chromosomal disorder. Relatives of individuals with these features and healthy controls will also participate. Subjects will be invited to participate in further behavioral studies in the future.

**SUBPROJECT PROGRESS:**

The purpose of this protocol is to establish a Behavioral Gene Bank, in which blood samples from patients with mental illness such as bipolar disorder and schizophrenia are collected for genetics research. This protocol was initially approved by the IRB on February 28, 2007 and was then IRB approved for annual continuation on 01/24/2008 (valid through 01/25/2009). A total of 32 subjects have been enrolled since July, 2007. An IRB approved recruitment brochure is posted on the GCRC website for the general public in the "current research" section. There have been no unexpected safety concerns. There are no publications as of yet. Proposed changes made to the protocol have been administrative only with no risk to participants.

**SPID:** 0647      **PROTOCOL:** 647      **TYPE:** RESEARCH

**SHORT TITLE:** Taste and Colon Cancer  
**LONG TITLE:** The Taste and Colon Cancer Collaboration Project

AIDS:	N	<b>TOTALS</b>	<u>A</u>	<u>B</u>	<u>D</u>
			Inpatient	0	0
<b>START DATE:</b>	1/18/2006	Scatter Bed	0	0	0
Total # pts expected for entire study:	200	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		

<b>INVESTIGATOR</b>	<b>DEPARTMENT</b>	<b>NON-HOST INSTITUTION: STATE, COUNTRY</b>
DUFFY, VALERIE PHD	ALLIED HEALTH SCIENCES	UConn, Storrs, CT USA
CONWAY, JUDITH ARNP	CANCER CENTER	
LEVINE, JOEL MD	Medicine	
SULLIVAN, BRIDGET MD	ALLIED HEALTH SCIENCES	UConn - Storrs, CT USA

#### SUBPROJECT DESCRIPTION:

New colon cancer cases in the US have increased 38% from 1950 to 2001, reaching over 106,370 in 2004 (1) and resulting in substantial morbidity and mortality. Colon cancer is an end result of a multiphase process. Aberrant Crypt Foci (ACF) appear to be the earliest identifiable neoplastic lesions in the colon (2) through use of magnifying chromoendoscopy. ACF may be detected in humans years before the appearance of neoplasms (2). Those that are dysplastic are most likely to progress to an adenoma (3), which is a pedunculate polypoid structure that grows into the lumen of the colon. Number of adenomatous polyps is considered the precursor of most large-bowel cancers. The genetics of colon cancer are very heterogeneous (4). Adenomas can occur sporadically or in readily defined high-risk groups, including those with family history of colon cancer or premalignant polyps. Although chemoprevention is being actively investigated (5-7), there is little at the present time to offer high-risk patients other than an increased watchfulness for malignant transformation. Strong epidemiologic and experimental data suggest that dietary factors play an important role in reducing the risk of colon cancer for genetically predisposed individuals (8), with as many as 7 in 10 cancers being preventable through diet and lifestyle changes (9). Diets that promote excess energy intakes, not the source of energy per se (8), and adiposity increase colon cancer risk (10), especially in men (11).

Risk of colon cancer varies genetically, which may explain why individuals who have the same dietary behaviors, vary in colon cancer risk. Polymorphisms in folate-metabolizing enzymes affect risk of colorectal neoplasia (22) with some genotypes deriving more benefit from diets rich in vegetable-related nutrients (23). Associations between colorectal cancer risk and meat consumption patterns and preparation varies with genetic differences in metabolism of heterocyclic amines, particularly to genetic variants in cytochrome p-450 and glutathione S-transferase activity (24). Higher intakes of vegetables also appears to decrease risk of spontaneous colon tumors, particularly in individuals who have mutations of the adenomatous polyposis colic gene (25).

Preliminary data suggests that another genetic variation in colon cancer risk involves genetic variation in taste. In a sample of 251 men, those who tasted PROP as more bitter had a higher number of polyps, but only among those who were years of age (26). Those who had polyps were most likely to be overweight/obese and, according to a subset of study sample, those who tasted PROP as most bitter reported lowest intake of vegetables.

#### SUBPROJECT PROGRESS:

There were no subjects enrolled during the report period and since initiation of the study because of staffing changes in the Colon Cancer Prevention Center. We are working to start data collection over the summer and to continue from that point.

**SPID:** 0648      **PROTOCOL:** 648      **TYPE:** RESEARCH

**SHORT TITLE:** Dietary Soy  
**LONG TITLE:** Metabolism and Bioavailability of Dietary Soy Isoflavones in Postmenopausal Women

AIDS:	N	TOTALS	A	B	D
			Inpatient	0	0
<b>START DATE:</b>	2/12/2007	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
BRUNO, RICHARD PHD, RD	NUTRITIONAL SCIENCES	UCONN STORRS, CT USA
KENNY, ANNE MD	Center on Aging	
KERSTETTER, JANE PHD	NUTRITION	UCONN - STORRS, CT USA

#### SUBPROJECT DESCRIPTION:

Postmenopausal women are at significantly higher risk for developing osteoporosis and cardiovascular disease. Hormone replacement therapy was suggested as a risk lowering, health promoting strategy for these chronic diseases among this high-risk female population. However, growing health concerns surrounding the use of hormone replacement therapy have resulted in the increased consumption of soy foods as an alternative natural therapy. Soy contains an abundant mixture of isoflavones, a class of flavonoids, which have phyto-estrogenic activities. The growing knowledge in this area has prompted a 15-fold escalation in soy food sales to \$4 billion dollars annually in comparison to the early 1990's. Despite the continued marketing of soy foods and their perceived health promoting benefits for postmenopausal women, there remains a lack of credible evidence that the consumption of these products will protect against the development of osteoporosis and/or cardiovascular disease. Moreover, the current paradigm regarding soy has shifted such that the intestinal metabolism of soy isoflavones to bioactive metabolites may dictate its benefits. Thus, in the absence of more thoroughly understanding the benefits of soy consumption and its metabolism in humans, useful dietary recommendations will not be possible. The long-term goal of our research program is to develop and evaluate dietary strategies that will

be effective in preventing and/or ameliorating oxidative stress-mediated processes implicated in the pathogenesis of chronic disease. The objective of this Donaghue Medical Research Foundation application is to define the mechanisms by which dietary soy consumption, as a complementary and alternative medical therapy, can favorably improve inflammatory and metabolic processes involved in bone and cardiovascular health in postmenopausal women. Our central hypothesis is that the metabolism profile of soy isoflavones will dictate an individual's response to specific biomarkers of bone and cardiovascular health. Our hypothesis is supported by our preliminary data indicating that 12-mo of daily soy consumption in postmenopausal women resulted in highly variable within-group responses with respect to bone mineral density and plasma lipoproteins. The lack of a uniform metabolic response suggests that other physiological factors, such as the variable metabolism of isoflavones by intestinal microflora, could potentially explain why select postmenopausal women had favorable biological responses whereas other did not. Our multi-disciplinary team is ideally positioned to undertake this important human health problem. Dr. R. Bruno (Principal Investigator) has been actively involved in studying the mechanisms by which phytonutrients contribute to human health and has experience in the analytical measurements of flavonoids and antioxidants from biological samples. In addition, Drs. J. Kerstetter (Consultant), K. Prestwood and A. Kenny are authorities in bone health and have already successfully conducted the 12-mo soy intervention trial in postmenopausal women from which our hypothesis has been formulated.

#### SUBPROJECT PROGRESS:

The underlying objectives of this project were to enable our critical understanding of the bioavailability of soy isoflavones on bone health and cardiovascular disease and to assess the potential protective effects of equol, a soy isoflavone metabolite, on these parameters. Indeed, a considerable body of epidemiological literature suggests a protective effect of soy consumption in post-menopausal women which has led to the hypothesis that soy isoflavones, the purported bioactive constituents of soy, exhibit estrogenic effects that protect against bone and cardiovascular disorders. Thus, the scope of this project was to evaluate serum soy isoflavones (daidzein and genistein) and a primary isoflavone metabolite (equol) in serum samples archived from a 12-mo prospective clinical trial where post-menopausal women (n = 97). The participants were randomized to daily dietary supplementation with A) control protein (20 g/d) + placebo, B) control protein (20 g/d) + 100 mg/d isoflavones, C) soy protein

(20 g/d) + placebo, or D) soy protein (20 g/d) + 100 mg/d isoflavones.

During this reporting period, we did not enroll any additional participants and we did not use the services of the UCHC GCRC. Thus, in the absence of any additional participant enrollment, there were no adverse events to report. Also, no procedural changes were made to this project from the original submission of this application.

We successfully developed a high sensitivity HPLC binary gradient separation method coupled with Coularray electrochemical detection (Figure 1) to obtain the necessary lower limits (~50 nmol/L) of detection required to assess serum isoflavones (daidzein, genistein, and equol) from free living individuals. In brief, serum isoflavone conjugates were hydrolyzed with  $\beta$ -glucuronidase and sulfatase, followed by sample protein precipitation with acetonitrile, delipidation with hexane. Subsequently, isoflavones were extracted with methyl-t-butyl-ether (MTBE), dried under nitrogen gas and then reconstituted in HPLC mobile phase prior to HPLC injection. The procedure has a linear operating range of 0.5-500 pmol injected ( $R^2 > 0.99$ ) for each analyte and the within day and between day CV of the assay was <8%.

This method was then utilized to examine serum concentrations of soy isoflavones from our study participants. Indeed, the use of this method enabled our ability to 1) assess compliance of the participants to their respective treatment or placebo, 2) determine serum isoflavone plasma responses, and 3) characterize the proportion of the study population who were equol (isoflavone metabolite) producers.

Data analysis for this project is actively underway. However, we are pleased to report that >95% of participants were compliant to the supplementation intervention regimen. We also established that ~40% of those assigned to the isoflavone supplements were equol producers. This is of particular importance because experimental evidence suggests that equol exhibits greater estrogen receptor binding activity than native soy isoflavones. Thus, we hypothesize that the equol producers in this study will have more favorable changes on health outcomes. Our currently statistical approaches are exploring the relationship of serum isoflavone concentrations and equol production with well established biomarkers of bone health, cardiovascular disease, and inflammation. We expect that these analyses will be completed during the next 3-mo and that up to three manuscripts will be submitted for publication in peer reviewed scientific journals during fall 2008.

<b>SPID:</b>	0651	<b>PROTOCOL:</b>	651	<b>TYPE:</b>	RESEARCH	
<b>SHORT TITLE:</b>	Secondary Syphilis					
<b>LONG TITLE:</b>	Adaptive Immunity in Secondary Syphilis					
<b>AIDS:</b>	N	<b>TOTALS</b>		<b>A</b>	<b>B</b>	<b>D</b>
		Inpatient		0	0	0
<b>START DATE:</b>	3/15/2007	Scatter Bed		0	0	0
Total # pts expected for entire study:	27	Outpatient		0	0	0
		Scatter RN Hours		0	0	0
		Offsite Visits		0	0	0
<b>RESEARCH BIONUTRITION</b>	N	<b>MULTICENTER STUDY</b>	N			
<b>INFORMATICS CORE</b>	Y	<b>CLINICAL TRIAL</b>	N			
<b>BIostatistician</b>	N	<b>CORE LAB</b>	N			
<b>ANCILLARIES ONLY</b>	N					

<b>INVESTIGATOR</b>	<b>DEPARTMENT</b>	<b>NON-HOST INSTITUTION: STATE, COUNTRY</b>
SALAZAR, JUAN MD	Pediatrics	

**SUBPROJECT DESCRIPTION:**

To examine aspects of the systemic adaptive cellular response to infection with *Treponema pallidum* in secondary syphilis patients.

**Specific Objectives:** To determine by intracellular cytokine staining the T. pallidum antigen specificity of circulating T cells in secondary syphilis patients. To determine if circulating T cells in secondary syphilis patients are undergoing apoptosis. To determine if T regulatory cells are increased in the blood of secondary syphilis patients. Adaptive Immunity in Secondary Syphilis. **Secondary Objective:** To compare the relative yield of T. pallidum genomic DNA (flaATAQMAN) by Real Time Quantitative Polymer Chain Reaction (PCR) assay between whole blood, plasma, serum and PBMC samples obtained from secondary syphilis patients.

**SUBPROJECT PROGRESS:****(A) Specific Aims:**

**Specific Aim 1.** To examine aspects of the local and systemic inflammatory response to infection with *Treponema pallidum* of particular relevance to HIV transmission and dissemination. This Aim was divided in two components: (a) to study the expression of HIV co-receptors in dermal inflammatory cells within syphilitic lesions and peripheral blood of patients with secondary syphilis and (b) to study the ex vivo effect(s) of T. pallidum on surface expression of HIV co-receptors by T-cells, macrophages and dendritic cells and how these changes influence HIV susceptibility and infectiousness.

**Specific Aim 2.** To establish the effect of early syphilis on viral load in patients with HIV co-infection. As previously agreed upon and reported in the previous year's progress report, the second Aim was eliminated. Instead we have significantly expanded Aim 1.

**(B) Studies and Results:**

**Specific Aim 1. Part (a):** This component has been completed and the results published in the Journal of Infectious Diseases (March 15, 2007). We demonstrated that dermal lesions from secondary syphilis patients contained a mixture of mononuclear cells, including T cells, monocytes/macrophages, and DCs, but no B cells. Lesional monocytes were larger and more granular and expressed high levels of CD14, indicating that these cells had differentiated into macrophages. Both CD11c<sup>+</sup> monocytoïd DCs (mDCs) and CD11c<sup>-</sup> plasmacytoïd DCs (pDCs) were present in dermal infiltrates and expressed the HIV chemokine co-receptor CCR5, which is also associated with leukocyte trafficking into inflamed skin. Both subsets expressed DC-SIGN, a member of the C-type lectin family which is linked with DC-T-Cell interactions and is a key HIV co-receptor. HLA-DR expression increases in mDCs but not pDCs, point to the primary role of this subset has in T. pallidum internalization and antigen presentation. Dermal infiltrates also had substantial numbers of memory and memory effector CD4<sup>+</sup> and CD8<sup>+</sup> T cells. Together these findings in skin confirmed that innate and adaptive immune responses co-evolve in tissues during active syphilitic infection setting the stage for local stimulation of T. pallidum-reactive lymphocytes. Our study also revealed the extent of immunophenotypic alterations of immune cells obtained from peripheral blood. Firstly, secondary syphilis patients displayed marked immunophenotypic modifications in circulating CD4<sup>+</sup> T cell subsets, supporting the notion that neosensitized T cells differentiate into memory, memory/effector, and effector subsets. These cells are probably trafficking from lymph nodes to sites of infection (i.e. skin) to interact with their cognate treponemal antigens. Secondly, we showed that over a third of circulating mDCs and pDCs expressed the HIV co-receptors, CCR5 and DC-SIGN. Circulating monocytes, similar to those in the dermis, also had increased CD14 MFI levels. It is our contention that these immunophenotypic changes in circulating monocytes and DCs occur as a result of their direct interaction with circulating spirochetes. **Part (b):** For this aim we have first examined the effects of spirochetes on monocytes and dendritic cells on PBMCs and isolated monocytes using an ex vivo model. We have already shown that spirochetes up regulate monocyte cell surface expression of the activation markers CD40 and CD83 and secretion of the proinflammatory

cytokines, TNF $\alpha$ , IL-6, and IL-1 $\beta$ . We have also demonstrated that for these events to occur the spirochetes need to be internalized and that in the case of *T. pallidum* internalization is critically dependent on the presence of human syphilitic sera. Results from these studies were published in collaboration with Meagan Moore, a talented MD/PhD student in Dr. Radolf's laboratory (see *Infection and Immunity* April, 2007). These have separate GCRC approval and the report has already been submitted by Dr. Radolf.

(C) Significance: Our published findings provide strong evidence that in the course of secondary syphilis, *T. pallidum* induces a potent innate and adaptive cellular immune response in both skin and peripheral blood. In accord with our underlying hypothesis, while this inflammatory response promotes clearance of the spirochete and may ultimately lead to some degree of resistance; it also provides an environment optimal for bidirectional transmission of HIV. The degree of innate and adaptive immune cell activation in peripheral blood also serves as a potential explanation for why individuals co-infected with HIV have demonstrable increases in HIV viral load. Finally, this research has also propelled the city of Cali's public health department to set up a campaign to improve diagnosis, treatment and follow-up of venereal syphilis. In addition, the collaboration has already improved gestational syphilis case ascertainment and a subsequent decrease in congenital syphilis cases.

There have been no safety concerns that would warrant changes in the protocol.

All clinical activities and enrollments take place at the study site in Cali, Colombia. However, the database for this study is still in development at the GCRC in collaboration with the investigator.



<b>SPID:</b>	0653	<b>PROTOCOL:</b>	653	<b>TYPE:</b>	RESEARCH	
<b>SHORT TITLE:</b>	PeriDial					
<b>LONG TITLE:</b>	Periodontal Infection, Depressive symptoms and inflammation in renal patients					
<b>AIDS:</b>	N	<b>TOTALS</b>		<b>A</b>	<b>B</b>	<b>D</b>
		Inpatient		0	0	0
<b>START DATE:</b>	3/31/2007	Scatter Bed		0	0	0
Total # pts expected for entire study:	50	Outpatient		46	0	0
		Scatter RN Hours		0	0	0
		Offsite Visits		19	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
IOANNIDOU, EFFIE DDS	Periodontology	
DONGARI-BAGTZOGLU, ANNA DDS, PHD	Periodontology	
KAPLAN, RICHARD PHD	Psychiatry	
LITT, MARK PHD	Behavioral Sci & Comm Hlth	

#### SUBPROJECT DESCRIPTION:

Periodontal diseases are chronic gram-negative oral infections initiated in the gingiva and leading to alveolar bone destruction and gradual loss of tooth supporting connective tissues. Cumulatively, these infections affect more than 70% of the general population. Recent evidence indicates that chronic severe periodontal disease is associated with systemically elevated inflammatory mediators. Chronic kidney disease (CKD) patients are also characterized by a chronic inflammatory state which contributes to an extremely high rate of atherosclerotic complications. Recently, both serum interleukin-6 (IL-6) and C-reactive protein (CRP) levels have been found to predict cardiovascular mortality in CKD patients on HD. We hypothesize that periodontal infections are highly prevalent in the CKD population and that both periodontal infections and depressive symptoms affect the systemic inflammatory status of HD and pre-dialysis CKD patients.

#### SUBPROJECT PROGRESS:

The overall aim of the study was to compare the periodontal status between the HD and control subjects and explore the relationship between hemodialysis, periodontal variables and systemic inflammation. The aim of these studies was also to collect preliminary data to support the K23 application and conduct appropriate power analyses. Participants received a complete clinical periodontal examination that included clinical attachment loss (CAL), probing depth (PD), plaque score (PS), bleeding on probing (BOP) and number of missing teeth. Venous blood was collected prior to clinical evaluation for quantification of serum IL-6 and CRP levels. Within 2 hours of blood collection, sera were separated after clotting for 30 minutes at 4°C followed by centrifugation at 3000xg for 15 minutes. Sera were analyzed in duplicate by enzyme-linked immunosorbent assay without knowledge of the periodontal disease or dialysis status of the participants. The assay analytical sensitivity was 2.0 pg/ml and the variation in IL-6 protein values within runs was less than 1%. The medical records of the HD patients were reviewed and all relevant information was collected using a standardized data extraction form.

So far we recruited 38 subjects. Overall, in the hemodialysis population, the mean age was 55.7 years, 46.2% were females, 33.3% were diabetic. When comparing the mean PD values between the two groups, HD subjects had higher, with a trend to significance, values than control subjects. Also, patients in the HD group showed more sites with BOP ( $p=0.50$ ) and higher PS ( $p=0.10$ ), although these were not statistically significant. When comparing the serum CRP levels between subjects with periodontitis vs. subjects without periodontitis, we found that the serum CRP levels were elevated with a trend to significance ( $p=0.1$ ) in the subjects with periodontitis. Moreover, the serum IL-6 levels in subjects with periodontitis were more elevated compared to the subjects without periodontitis although they didn't reach statistical significance ( $p=0.4$ ).

Although supportive of the hypothesis to be further tested in the proposed work, accurate interpretation of these preliminary data is prohibited by the small sample size, which does not permit examination of confounding factors such as diabetes, concurrent NSAID use, dialysis vintage or other systemic factors that may influence CRP and IL-6 levels in this population. Therefore, we are proposing to conduct a larger scale study to examine the periodontal status of HD and pre-dialysis CKD patients and take into account all relevant comorbidities, so that we can accurately assess the influence of periodontal infections in their systemic inflammatory status.

**SPID:** 0654      **PROTOCOL:** 654      **TYPE:** RESEARCH

**SHORT TITLE:** Estradiol Therapy  
**LONG TITLE:** Pilot study on the Effect of Short Term Estradiol Therapy on Osteoclastogenesis from Human Peripheral Blood Mononuclear Cells in Postmenopausal Women

AIDS:	N	TOTALS	A	B	D
		Inpatient	0	0	0
<b>START DATE:</b>	3/31/2007	Scatter Bed	0	0	0
Total # pts expected for entire study:	12	Outpatient	7	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
MIRZA, FARYAL MD	Medicine	
LORENZO, JOSEPH MD	Medicine	
RAISZ, LAWRENCE G MD	Medicine/Endocrinology	
TAXEL, PAMELA MD	Medicine	

#### SUBPROJECT DESCRIPTION:

The mechanism of increased bone resorption with estrogen is not fully understood, but there is good evidence for effects on osteoclastic precursors of the hematopoietic lineage, and on the osteoblastic cells of mesenchymal lineage that interact with hematopoietic cells to produce osteoclasts. Circulating osteoclast precursors have been clearly demonstrated in peripheral blood, and there is some evidence for circulating osteoblast precursors as well 2. We have shown that short term estrogen treatment can alter the expression of receptor activator of NF $\kappa$ B ligand (RANKL) indicating an effect on the osteoblastic lineage, and the response to macrophage colony stimulating factor (M-CSF) and RANKL, indicating an effect on hematopoietic lineage. Initial aim of this study will be to analyze osteoclastogenesis in peripheral blood before and after estrogen treatment, when M-CSF, RANKL and other direct stimulators of osteoclastogenesis are added, thus testing the effects on hematopoietic lineage. RANKL expression will also be measured, and if changes are observed, then additional studies to isolate and analyze effects of estrogen on cells of osteoblastic lineage can be carried out.

#### SUBPROJECT PROGRESS:

Peripheral blood osteoclastogenesis is being studied in postmenopausal and premenopausal women. We started out with postmenopausal women and tested changes in multiple aspects of our protocol (including plating density, Ficoll preparation, type of centrifugation, type of culture plate, duration of culture) until we were successful in making large numbers of osteoclasts in vitro. A considerable variability was noted in the postmenopausal and in the premenopausal women for reproducibility of these assays, although premenopausal women had more robust osteoclastogenesis. Currently we are using various methods including flow cytometry and antibody labeled beads to better identify and isolate the CD14 monocytes that serve as precursors of the osteoclasts to minimize variability in these assays. We think that reproducible differences between pre- and postmenopausal women would be useful preliminary data for applying for other grants.

**SPID:** 0655      **PROTOCOL:** 655      **TYPE:** RESEARCH

**SHORT TITLE:** Otoacoustic Emissions  
**LONG TITLE:** Rapid Method for Collection of Stimulus Frequency Otoacoustic Emissions

AIDS:	N	TOTALS	A	B	D
		Inpatient	0	0	0
<b>START DATE:</b>	3/31/2007	Scatter Bed	0	0	0
Total # pts expected for entire study:	20	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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PARHAM, KOUROSH MD	Surgery	
DUCK, KIM PHD	Surgery	

#### SUBPROJECT DESCRIPTION:

Otoacoustic emissions (OAEs) are sounds generated by the inner ear and their properties have been used to assess inner ear function. There are a number of ways of eliciting and measuring OAEs, e.g., click-evoked OAEs or distortion product OAEs. Both of these techniques are currently in use clinically, however, it is recognized that both have shortcomings (i.e., poor frequency specificity in the case of click-evoked and as yet indeterminate site of DPOAE generation thus unclear correlation with site of cochlear pathology in the case of DPOAEs). Stimulus frequency otoacoustic emissions (SFOAEs) offer the most frequency specific method of assessing function along the cochlear partition. Up to now measurement of SFOAEs has been too time consuming to allow use in clinical applications. We have developed a rapid method for recording stimulus frequency otoacoustic emissions (SFOAEs). Here we propose to develop this technique into a useful clinical tool with potential to replace CEOAEs and DPOAEs, and obtain normative data and preliminary results from hearing impaired listeners.

#### SUBPROJECT PROGRESS:

We tested 8 subjects this year. All subjects underwent audiometric evaluation and fulfilled inclusion criteria. Additionally, all were tested using the novel stimulus frequency otoacoustic emissions. No safety concerns were encountered. The preliminary results demonstrating our technical capability was presented at the annual meeting of the Association for Research in Otolaryngology in February 2008. Since February 2008 we have not collected any further data because of increased clinical demand on the Principal Investigator (PI). Currently, data collection and analysis are on hold pending IRB continuation. If our data analysis suggests we have gathered sufficient results from normal hearing ears to establish a baseline for our measures, we may propose to test some hearing impaired subjects to assess sensitivity and specificity of our novel method as a diagnostic tool. We will, of course, apply for IRB modification and GCRC approval prior to proceeding. We are not likely to take these steps until late July 2008 when the clinical load on the PI is expected to decrease.

**SPID:** 0656      **PROTOCOL:** 656      **TYPE:** RESEARCH

**SHORT TITLE:** HSMMP656

**LONG TITLE:** Adiposity, Insulin-like growth factor system, and colonic polyps

	AIDS:	N	<b>TOTALS</b>	<u>A      B      D</u>		
				Inpatient	0	0
<b>START DATE:</b>		3/31/2007	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	Y	CLINICAL TRIAL	N
BIostatistician	N	CORE LAB	N
ANCILLARIES ONLY	N		

<b>INVESTIGATOR</b>	<b>DEPARTMENT</b>	<b>NON-HOST INSTITUTION: STATE, COUNTRY</b>
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SWEDE, HELEN PHD	Community Medicine	
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STEVENS, RICHARD G PHD	Community Medicine	
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**SUBPROJECT DESCRIPTION:**

Excess body fat (i.e., adiposity) has been implicated as a primary risk factor for colorectal cancer (CRC), but the precise physiological mechanisms underlying this relationship remain largely unknown. Adiposity frequently triggers the insulin resistance syndrome, a hallmark of which is a dysregulated Insulin-like Growth Factor (IGF) system. IGFs are potent mitogens that play a pivotal role in cellular renewal and apoptosis. A growing body of pre-clinical and epidemiologic evidence links various IGF abnormalities with CRC risk. A few epidemiologic studies have examined the association between circulating IGF abnormalities and colonic polyps, yet this relationship has not been fully explored. The specific aims of the proposed study aims are to examine features of polyps (number, size, histology) in relation to: 1) Circulating markers of insulin resistance (i.e., fasting levels of: IGF-1, IGF-2, IGF binding protein 3, insulin and glucose; and, 2) Circulating proinflammatory cytokines (CRP, tumor necrosis factor-alpha.) We will examine these relationships in a sample of 80 non-diabetic patients receiving colonoscopy at UCHC. Should the impact of biochemical abnormalities related to insulin resistance be observed in early colonic lesions, it would offer new insights into CRC etiology and strengthen the evidence base about CRC prevention related to excess body fat.

**SUBPROJECT PROGRESS:**

A project initiation was held, and an Institutional Review Board (IRB) application was submitted but the study was closed out in early 2008 due to delays in starting patient recruitment as a result of a medical leave by the study gastroenterologist as well as other staffing gaps. Subsequently, the project was subsumed into GCRC # 674 (Swede, PI) due to common research aims.

**SPID:** 0657      **PROTOCOL:** 657      **TYPE:** RESEARCH

**SHORT TITLE:** Expressive Writing  
**LONG TITLE:** Pilot Study of the Effects of Expressive Writing on Endothelial Function

AIDS:	N	TOTALS	A	B	D
		Inpatient	0	0	0
<b>START DATE:</b>	3/31/2007	Scatter Bed	0	0	0
Total # pts expected for entire study:	20	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	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	
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TENNEN, HOWARD PHD	Community Medicine	
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#### SUBPROJECT DESCRIPTION:

Our group has been investigating associations between history of depression and mental stress on the one hand, and endothelial function on the other hand, in postmenopausal women. To date we have found that relative to their never depressed counterparts, women with a history of depression show impaired resting endothelial function. The association between history of depression and resting endothelial dysfunction is especially strong in women with type 2 diabetes. Preliminary data from our group also suggest that women with a history of depression may show more endothelial dysfunction in response to an acute stressor than their never depressed counterparts. Our group is now interested in testing interventions to improve resting endothelial function, and endothelial stress reactivity, in women at risk for endothelial dysfunction. Expressive writing interventions have shown benefits for a variety of health and mental health outcomes in healthy, medical, and psychiatric samples. This pilot and feasibility study will explore the effects of an expressive writing intervention on endothelial function in women with diabetes. Twenty women will participate, who will be recruited as part of GCRC study #453. History of depression and current depressive symptoms will be assessed at baseline. Resting endothelial function and endothelial stress reactivity will be assessed at baseline using brachial artery flow-mediated dilation (FMD). Participants will then be randomized to either an expressive writing condition, or a control writing condition. Women in the expressive writing condition will write about the facts and emotions related to a personal trauma or upsetting event. Women in the control writing condition will write about assigned topics devoid of emotional content (e.g., fashion, daily tasks, shopping lists). All participants will complete twice-weekly writing sessions for 4 weeks. Participants writing exercises will be mailed to the investigator so that the postmark can verify compliance with the writing schedule. One month after the last writing exercise, participants will return for follow-up resting FMD and FMD stress reactivity assessments. We hypothesize that relative to the women in the control writing condition, women in the expressive writing condition will show improvement in resting FMD and FMD stress reactivity. We further hypothesize that depression history will modify the effect of the intervention such that women with a history of depression will benefit more from the intervention than their never depressed counterparts. We recognize that we will be underpowered to detect significance; the goal of this pilot is to detect trends in the hypothesized directions. The specific aims are to: 1) estimate an effect size to be used in a power analysis for a subsequent external grant proposal; 2) address the acceptability of the protocol for this population; 3) gather participant feedback to be used to modify the intervention for future proposals.

#### SUBPROJECT PROGRESS:

From 4/1/2007 until 3/31/2008 (and since initiation of the study), 3 women enrolled. One withdrew from the study citing time commitments, one is currently participating, and one has completed. No modifications were made to this pilot study. There were no expected safety concerns for this study. The study began enrolling in February of 2008, and there are no publications at this time.

<b>SPID:</b> 0658	<b>PROTOCOL:</b> 658	<b>TYPE:</b> RESEARCH
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<b>SHORT TITLE:</b>	AICD (Activation Induced Cell Death)
<b>LONG TITLE:</b>	Rescuing CTL from Activation Induced Death

AIDS:	N	TOTALS	A	B	D
		Inpatient	0	0	0
<b>START DATE:</b>	4/19/2007	Scatter Bed	0	0	0
Total # pts expected for entire study:	12	Outpatient	38	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	
CLARK, ROBERT MD	Immunology	
DORSKY, DAVID MD	Infectious Disease	

**SUBPROJECT DESCRIPTION:**

This project is designed to examine the molecular mechanism underlying suicidal death in tumor antigen specific cytolytic T lymphocytes (CTL) when they re-encounter antigen and to examine how such deaths in the CTL can be prevented so as to orchestrate a robust and long-lived CTL response during cancer immunotherapy. The studies will be done in ex-vivo laboratory experiments and in animals bearing grafts of human melanoma cells.

**SUBPROJECT PROGRESS:**

Number of subjects entered - 15  
 There has been no change in the recruitment plan  
 There has been no unexpected safety concern  
 Experiments and Data analysis are continuing  
 No change in the protocol

<b>SPID:</b> 0659	<b>PROTOCOL:</b> 659	<b>TYPE:</b> RESEARCH
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<b>SHORT TITLE:</b>	HIV on Hepatitis C
<b>LONG TITLE:</b>	Impact of HIV on Hepatitis C Infection in Hemophilia

	AIDS:	Y	TOTALS	A	B	D
			Inpatient	0	0	0
<b>START DATE:</b>		4/19/2007	Scatter Bed	0	0	0
Total # pts expected for entire study:		9	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	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:**

This study is being done at hemophilia centers throughout the United States. The purpose of this study is to collect medical information, blood samples and liver tissue samples from study subjects with hemophilia and hepatitis C (HCV). The major aim of the study is to find how frequently individuals with hemophilia develop cirrhosis (liver scarring) from chronic hepatitis C infection, and whether co-infection with human immunodeficiency virus (HIV) may worsen liver disease outcome due to their hepatitis C.

**SUBPROJECT PROGRESS:**

One subject was enrolled into this study during the reporting period and since initiation of the study. There are no recruitment plans as the study has been closed. The IRB closed this study effective as of 11/26/07. Our study subject did not experience any adverse events during the time of his study participation. The study site has not given us any interim data or outcomes for this study.

<b>SPID:</b> 0660	<b>PROTOCOL:</b> 660	<b>TYPE:</b> RESEARCH
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<b>SHORT TITLE:</b>	Effects of Tobacco
<b>LONG TITLE:</b>	The Effects of Tobacco on Brain Structure and Function are Amplified by Genotype

AIDS:	N	TOTALS	A	B	D
			Inpatient	0	0
<b>START DATE:</b>	5/17/2007	Scatter Bed	0	0	0
Total # pts expected for entire study:	100	Outpatient	19	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
BAUER, LANCE PHD	Psychiatry	
COVAULT, JONATHAN MD, PHD	Psychiatry	
PEARLSON, GODFREY MD	PSYCHIATRY	INSTITUTE OF LIVING, CT USA

#### SUBPROJECT DESCRIPTION:

Red peppers (*Capsicum frutescens*) have been used for several thousand years as food additives and for a broad variety of medical applications in Indian, Native American, African and Chinese medical traditions. CP is the pungent component of red peppers. Chemically, it is a derivative of vanillyl amide, 8-methyl-N-vanillyl-6-noneamide and has a molecular weight of 305.42. The receptor for CP is vanilloid receptor 1 (VR1). VR1 has been shown to be highly expressed in nociceptive neurons of dorsal root and trigeminal ganglia. CP binds to VR1 on sensory neurons to convey the sensation of pain. Apart from its neurological functions CP has also been shown to be active immunologically, in generating more antibody-producing cells compared to untreated controls. Dietary CP in BALB/c mice has been shown to enhance lymphocyte proliferation and serum immunoglobulin levels. Inhalation of CP has been shown to interfere with neural responses involved in inflammation in the lungs of Lewis rats and such interference modulates immunity to inhaled antigens. We and others have observed that mouse and human dendritic cells (DCs), a key cell type in immune responses, have the receptor for CP, and engagement of this receptor has powerful immune consequences. Our recent data suggest that intra-lesional administration of CP into a preexisting murine tumor results in retarded progression of the injected tumor regardless of whether the tumor is at its early or late stage. Further, it leads to significant inhibition of growth of other, un-injected tumors in the same animal. We have shown that only tumor cells but not normal cells undergo apoptosis in response to CP but CP elicited anti-tumor immunity is T cell mediated and tumor-specific. CP has been used previously in clinical studies. Intradermal and topical application of CP has been used to study mechanisms of allodynia and hyperalgesia and the efficacy of drugs in relieving the symptoms. The dose of CP varied from 20 to 250 µg. Pain intensity and vital signs were monitored after CP administration. We have used intra lesional CP in mouse tumor model with MTD at a dose of 200 µg. The common toxicity noticed was scar at the injection site. Based upon our observations in the laboratory, we have hypothesized intra lesional use of CP in patients with melanoma may have immunological relevance in this disease.

#### SUBPROJECT PROGRESS:

The general goal of the activity is to provide data regarding structural and functional brain abnormalities in middle-aged adults at increased genetic and environmental risk for cerebrovascular disease. The activity is a clinical research project to be completed within a one year period. The list of objectives includes the recruitment of 100 adults varying in risk as defined by the presence versus absence of a history of heavy tobacco use. Each of these groups will be further stratified by ApoE-e4, Factor XIII Val34Leu, and Paraoxonase-1 Gln192Arg genotypes in separate analyses. High resolution structural magnetic resonance images will be collected of the whole brain. In addition, evoked electroencephalographic responses and cognitive test performance will be recorded to determine whether the MRI abnormalities are physiologically significant. The primary analyses will examine the independent and interactive effects of smoking and genotype."

As of this date (with 4 quarters of funding remaining), we have enrolled and tested 24 study participants. With the initial delays associated with hiring study personnel and receiving approvals from 3 separate IRB/human subjects committees (at University of Connecticut Health Center (UCHC), Institute of Living/Hartford Hospital (IOL/HH), and the Connecticut Department of Public Health (CT DPH)) now passed, we foresee no barriers in meeting future enrollment targets. We are recruiting participants from



multiple sources. Of course, at this early stage of data collection, we have no findings to report.

<b>SPID:</b> 0661	<b>PROTOCOL:</b> 661	<b>TYPE:</b> RESEARCH
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**SHORT TITLE:** FMSclerostin

**LONG TITLE:** Comparison of Serum Levels of Sclerostin in Premenopausal and Postmenopausal Women

AIDS:	N	TOTALS	A	B	D
		Inpatient	0	0	0
<b>START DATE:</b>	5/17/2007	Scatter Bed	0	0	0
Total # pts expected for entire study:	40	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
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MIRZA, FARYAL MD	Medicine	
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#### SUBPROJECT DESCRIPTION:

Osteocytes inhibit bone formation by secreting sclerostin, a peptide which is a product of the SOST gene and a negative regulator of osteoblasts (1, 2). Once secreted, sclerostin is transported to the osteoblasts on the bone surface, where it regulates their function. Sclerostin has been shown to inhibit osteoblast development in vitro by inhibiting proliferation, as well as early and late stages of osteoblast differentiation, in both mouse and human osteogenic cells. Sclerostin also stimulates osteoblast apoptosis (3). In sclerosteosis, the inhibitory effect of sclerostin is absent due to mutations in the SOST gene, which results in an increase in bone mass as a result of increased bone formation.

#### SUBPROJECT PROGRESS:

Number of premenopausal women enrolled during report period is 9.

Number of premenopausal women enrolled since beginning of study is 12, of those 3 are presently active. There are 2 more scheduled to start in May of 08.

Number of postmenopausal women enrolled since beginning of the study is 25. Of those 3 were found to be not eligible, 2 were lost to follow-up. 20 completed the study.

We are doing well with recruitment. 25 postmenopausal women have been recruited for the study, of which 20 completed the study. 12 premenopausal women have been enrolled in the study so far and we anticipate that we may complete enrollment by the end of June, 2008.

No safety concerns have been reported to date. There are no publications as yet.

<b>SPID:</b> 0662	<b>PROTOCOL:</b> 662	<b>TYPE:</b> RESEARCH
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<b>SHORT TITLE:</b>	Pharmacogenetics of Warfarin
<b>LONG TITLE:</b>	Pharmacogenetic Testing for Warfarin Therapy

	AIDS:	N	<b>TOTALS</b>	<u>A</u> <u>B</u> <u>D</u>		
				Inpatient	0	0
<b>START DATE:</b>		6/21/2007	Scatter Bed	0	0	0
Total # pts expected for entire study:		150	Outpatient	143	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		

<b>INVESTIGATOR</b>	<b>DEPARTMENT</b>	<b>NON-HOST INSTITUTION: STATE, COUNTRY</b>
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FANG, MIN MD, PHD	Genetics & Dev. Biology	
BONA, ROBERT MD	Medicine/Hem-Onc	

**SUBPROJECT DESCRIPTION:**

Pharmacogenetics is a new and rapidly evolving discipline. The goal is to enhance efficacy and safety by applying genetic information to clinical administration of medications. Warfarin, an anticoagulant, is one of the most common prescription medications worldwide. As much as it is a life-saver, warfarin can also pose high risk of morbidity and mortality. Major bleeding episodes happen in ~7% of patients. Current dosing algorithms do not account for genetic factors. Recent studies have shown strong evidence that individuals with certain genetic variants require lower doses. The Federal Drug Administration (FDA) has proposed drug label changes for warfarin. And the National Academy of Clinical Biochemistry (NACB) has drafted guidelines and recommendations for pharmacogenetic testing in general. Currently, the Department of Health & Human Services (HHS) posted a draft report of the Secretary's Advisory Committee on Genetics, Health, and Society for public comments until June 1, 2007. This report recommended that the FDA work with professionals to develop dosing guidelines, encourage clinical trials exploring the relationships between diagnostics and drug response, and to translate the findings from prospective studies into treatment guidelines. We have successfully employed the Invader technology to develop a genotyping assay for patients under warfarin treatment. To determine the clinical performance characteristics of this test, we propose this protocol to retrospectively genotype patients under warfarin therapy. New algorithms of warfarin dosing determination will be evaluated. This study will pave the way for clinical implementation of randomized prospective clinical research on warfarin dosing accuracy, cost effectiveness, and patient burden reduction.

**SUBPROJECT PROGRESS:**

- Number of subjects enrolling during the report period and since initiation of the study: 150
- Any changes in recruitment plans that might be needed : No
- Unexpected safety concerns and their resolution : No
- Interim data and outcomes if appropriate: We found that pharmacogenetics information is helpful for warfarin dose prediction. However, the published algorithm from the UK group needs minor adjustment when applied to our population, especially regarding the parameter of height. Data analysis is underway.
- Any proposed changes made or anticipated in the protocol: No.
- Publications: manuscript in preparation. Will cite GCRC funding number

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**SPID:** 0663      **PROTOCOL:** 663      **TYPE:** RESEARCH
 

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**SHORT TITLE:** Bone Health  
**LONG TITLE:** Bone Health in Women with Breast Cancer on Aromatase Inhibitors
 

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AIDS:	N	TOTALS	A	B	D
		Inpatient	0	0	0
<b>START DATE:</b>	6/21/2007	Scatter Bed	0	0	0
Total # pts expected for entire study:	55	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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TAXEL, PAMELA MD	Medicine	
MIRZA, FARYAL MD	Medicine	

**SUBPROJECT DESCRIPTION:**

Aromatase Inhibitors (AIs) are a class of compounds that inhibit the synthesis of estrogens from androgens by blocking the Cytochrome P-450 Enzyme Aromatase which catalyzes the conversion of androgens to estrogens in the peripheral tissue (adipose tissue, bone, vascular endothelium, brain and breast tumors). They will effectively reduce the amount of circulating estrogens and therefore play a powerful role in treatment of estrogen and progesterone- receptor sensitive breast cancer patients. Because they cause a marked reduction in serum estrogen level, women treated with such agents are at an increased risk of developing osteoporosis and bone fractures, as many clinical trials have reported. In the Bone Health Service of the Cancer Center at University of Connecticut Health Center, we have been evaluating women who will receive AI's for breast cancer. In preparation for a randomized controlled trial, we propose to evaluate parameters of bone health in this population.

**SUBPROJECT PROGRESS:**

This project is currently completing data entry and analysis with the assistance of the General Clinical Research Center (GCRC) statistician.

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**SPID:** 0664      **PROTOCOL:** 664      **TYPE:** RESEARCH

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**SHORT TITLE:** 3RS  
**LONG TITLE:** Behavioral and Physiological Responses to Race-Related Stress in Diabetic Women

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AIDS:	N	TOTALS	A	B	D
		Inpatient	0	0	0
<b>START DATE:</b>	9/20/2007	Scatter Bed	0	0	0
Total # pts expected for entire study:	80	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	Y
ANCILLARIES ONLY	N		

INVESTIGATOR	DEPARTMENT	NON-HOST INSTITUTION: STATE, COUNTRY
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WAGNER, JULIE PHD      Behavioral Sci & Comm Hlth

**SUBPROJECT DESCRIPTION:**

The broad goal of this project is to establish evidence that race-related stress is associated with physiological and behavioral processes that may contribute to the disproportionate rates of diabetes complications among African American women. We propose studying the effects of racial stress on blood pressure, glycemia, insulin sensitivity, and diabetes self-care important factors which underlie most, if not all, complications. We propose investigating experimentally induced racial stress and day-to-day, self-reported racial stress.

**SUBPROJECT PROGRESS:**

During this period, equipment was ordered and staff was trained to administer the components of this study. Enrollment for the study began in February, 2008. From initiation to 3/31/2008, 5 women enrolled and completed the study. An additional 30 participants have been screened and scheduled for enrollment after 4/1/2008. Several modifications to the project approved by IRB this year include:

There are no unexpected safety concerns. There are no publications at this time.

<b>SPID:</b> 0665	<b>PROTOCOL:</b> 665	<b>TYPE:</b> RESEARCH
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<b>SHORT TITLE:</b>	Topiramate Treatment
<b>LONG TITLE:</b>	Topiramate Treatment of Problem Drinkers

	AIDS:	N	<b>TOTALS</b>			
				A	B	D
			Inpatient	0	0	0
<b>START DATE:</b>		10/23/2007	Scatter Bed	0	0	0
Total # pts expected for entire study:		192	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		

<b>INVESTIGATOR</b>	<b>DEPARTMENT</b>	<b>NON-HOST INSTITUTION: STATE, COUNTRY</b>
KRANZLER, HENRY MD	Psychiatry	
ARMELI, STEPHEN PHD		PACE UNIVERSITY, NY USA
ONCKEN, CHERYL MD	Medicine	
TENNEN, HOWARD PHD	Community Medicine	

#### SUBPROJECT DESCRIPTION:

The proposed study is a 12-week trial comparing topiramate (TOP), at a dosage of 200 mg/day, with an inactive placebo. We will randomly assign 160 problem drinkers (i.e., heavy drinkers without evidence of physical dependence on alcohol) who want to reduce their drinking. It is estimated that 30% of the general population are problem drinkers (NIAAA 2007). Despite its high prevalence, problem drinkers are understudied, particularly with respect to medications that may help them to reduce their drinking to safe levels. The study will extend to this patient population findings from a trial of TOP, which showed the drug to be well tolerated and efficacious in moderately-severe alcohol-dependent patients (Johnson et al. 2003). The aims of the present study are to examine: 1) TOP's safety and efficacy in reducing drinking and heavy drinking, 2) the relations among medication, daily mood, expectancies, and drinking behavior, and 3) the durability of TOP's effects during a six-month post-treatment follow-up period. A fourth, exploratory aim, is to estimate the effect size of variation in genes encoding GABA and glutamate receptors as moderators of both the therapeutic and adverse effects of TOP. A fifth aim is to examine allelic and haplotypic association to alcohol use disorders and related behavioral and psychiatric phenotypes by examining variants in genes that have been implicated in the pathophysiology or risk of these behaviors or disorders. The study will use interactive voice response technology to collect daily measures of drinking, mood, and medication usage. Biological measures of alcohol consumption (i.e., GGTP and CDT) will be used to validate self-reports. Hierarchical linear modeling will be used to examine effects at the between-person and within-person levels of analysis. Careful evaluation of the study's hypotheses will provide important information on the efficacy and mechanism of effects of TOP as a treatment for problem drinkers.

#### SUBPROJECT PROGRESS:

Subject enrollment began in March 2008. A total of 3 subjects were enrolled during the report period (a total of 3 since initiation of the study). No changes in recruitment plans are needed at this time. There have been no unexpected safety concerns associated with this study. Interim data are not available since data collection is ongoing. This study uses interactive voice response technology (IVR) for daily data collection, with support from the General Clinical Research Center (GCRC). Since this study was originally approved we made the following changes in the protocol (all changes IRB-approved): 1) the Medical Management counseling session manual was finalized and underwent IRB review (including a new subject handout used during the counseling sessions: Quick Reference Medication Grid); 2) the Research and Development (RAND) 36-Item Health Survey replaced the Short Form (SF)-36 in the battery of study questionnaires; 3) the up-titration medication schedule was modified to state (where applicable) that instead of two 25 mg capsules, one 50mg capsule will be used. This will help reduce medication costs, and use of a 50 mg dosage in this manner has been well tolerated in other clinical trials of topiramate; 4) we updated the description of the counseling session monitoring and feedback plan; 5) we added information to the protocol regarding topiramate's potential effects on hormonal birth control (i.e., that topiramate may make some types of hormonal contraceptive methods less effective; and, that women should report any changes in their bleeding patterns to the study clinician); 6) we added a statement to the consent form asking participants to allow us to audiotape the counseling sessions and we added information regarding topiramate's potential effects on hormonal birth control; 7) As per UConn Health Center (UHC) Institutional Review Board (IRB) guidance, the HIPAA Authorization was revised with the new UHC template; 8) the IVR Script and Wallet Card were modified to update language describing the collection of drinking, smoking, and medication data.; 8) addition of a co-investigator (Carolyn Drazinic); 9) edits to

IVR script (during preliminary testing of the IVR telephone script, we found some areas of the script needing small edits in order to improve the flow of questioning. The content of the information being collected has not changed and no new questions were added to what was previously IRB-approved. Due to the edits we made to the script, the following subject handouts and forms were modified so that they are consistent with the IVR script to be used during the conduct of the study: IVR Follow-Along Sheet IVR Wallet Card, and IVR Information Form); 10) We updated some study questionnaires to add the visit number to the heading (in order to facilitate data entry) and study documents used with the Pharmacy to add the study abbreviation ("Top/Alc"), which will help identify the study for Pharmacy staff; 11) we modified the parameters to be used to randomize subjects into groups for assignment to placebo vs. topiramate: we removed the variable "drinking days" and added the variables "drinks per drinking day" and "number of DSM-IV alcohol dependence symptoms". The variable "heavy drinking days" was changed to "percent heavy drinking days". All data were already being collected under IRB-approved protocol, so no changes are necessary to the information being collected from subjects. We updated the protocol and URN form to reflect these changes.

**SPID:** 0666      **PROTOCOL:** 666      **TYPE:** RESEARCH

**SHORT TITLE:** Radiation-induced Mucositis  
**LONG TITLE:** Anti-Inflammatory Intervention in Radiation-induced Oral Mucositis

AIDS:	N	TOTALS	A	B	D
			Inpatient	0	0
<b>START DATE:</b>	11/15/2007	Scatter Bed	0	0	0
Total # pts expected for entire study:	9	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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LALLA, RAJESH BDS, PHD	Oral Diagnosis	
PETERSON, DOUGLAS DMD, PHD	Oral Diagnostics	

#### SUBPROJECT DESCRIPTION:

Head and neck cancer accounts for 5 to 40% of all malignancies, depending on geographical location in the world. Most head and neck cancer patients are treated with radiation therapy (RT) in combination with surgery and/or chemotherapy. Almost 100% of patients treated for head and neck cancer, with radiation therapy to fields involving the oral cavity, develop erythematous, erosive and ulcerative lesions of the oral mucosa referred to as oral mucositis. These lesions are extremely painful, compromise nutrition and quality of life and may necessitate interruptions in RT, thus adversely affecting cancer therapy outcomes 1, 2. Thus, the literature defines oral mucositis as the major dose-limiting toxicity of RT to the head and neck region. Significant evidence implicates inflammatory responses to RT in the pathogenesis of oral mucositis 3. Evidence available to date supports the investigation of anti-inflammatory agents in this condition. More specifically, evidence supports the testing of a corticosteroid mouthrinse to reduce the severity of radiation-induced oral mucositis. However, with the exception of one small uncontrolled study 4 which indicated impressive efficacy, topical corticosteroids have not been formally evaluated for this condition. This constitutes an important gap in knowledge because oral mucositis is the single most debilitating complication of radiation therapy for head and neck cancer. Our long-term goal is to identify effective therapeutic interventions to reduce mucosal injury and pain in radiation-induced oral mucositis. The objective of this application is to conduct a Phase I study that will provide information necessary to design an extramurally-funded, randomized, placebo-controlled trial testing the effects of a topical corticosteroid mouthrinse on radiation-induced oral mucositis.

#### SUBPROJECT PROGRESS:

This study received initial IRB approval on 01/22/2008. There were no subjects enrolled on this study for the period 4/1/07-3/31/08. There are no changes in recruitment plans for this study.

There have been no unexpected safety concerns identified since the initiation of this study. There has been no data collected through 3/31/08.

There are no planned modifications to the protocol at this time.



<b>SPID:</b>	0667	<b>PROTOCOL:</b>	667	<b>TYPE:</b>	RESEARCH	
<b>SHORT TITLE:</b>	Albuterol					
<b>LONG TITLE:</b>	Genetic Influences of Albuterol Responsiveness in Children with Bronchiolitis					
<b>AIDS:</b>	N	<b>TOTALS</b>		<b>A</b>	<b>B</b>	<b>D</b>
		Inpatient		0	0	0
<b>START DATE:</b>	11/21/2007	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
<b>RESEARCH BIONUTRITION</b>	N	<b>MULTICENTER STUDY</b>		N		
<b>INFORMATICS CORE</b>	Y	<b>CLINICAL TRIAL</b>		N		
<b>BIostatistician</b>	N	<b>CORE LAB</b>		N		
<b>ANCILLARIES ONLY</b>	N					

<b>INVESTIGATOR</b>	<b>DEPARTMENT</b>	<b>NON-HOST INSTITUTION: STATE, COUNTRY</b>
CARROLL, CHRISTOPHER MD	PEDIATRICS	CONNECTICUT CHILDREN'S MEDICAL, CT USA

#### SUBPROJECT DESCRIPTION:

Bronchiolitis is a significant cause of morbidity and hospitalization in children, accounting for approximately 125,000 hospitalizations per year in the U.S. Of these hospitalized children, 8% will require ICU admission and 67% of these children will require mechanical ventilation. Mortality in previously healthy children is generally low, however, in children with high-risk medical conditions such as prematurity or congenital heart disease, mortality can be as high as 3%. In addition, bronchiolitis infections are associated with long term respiratory problems including development of recurrent wheezing, airway hyper-reactivity, and asthma. Despite four decades of clinical trials, there are no therapies demonstrated to be effective in shortening either hospitalization or length of intensive care stay in children with bronchiolitis. Treatment for this disease is largely supportive. Current controversies involve the utility of bronchodilators, steroids, antiviral therapies, and immunoprophylaxis. Other attempted therapies include nebulized hypertonic saline, atrovent, nebulized deoxyribonuclease I (pulmozyme), and inhaled nitric oxide. Although a mixture of these therapies are used in children with bronchiolitis based on individual provider preference, none have been definitively shown to improve outcomes in children with bronchiolitis. Recently, investigators have shown that genetic factors have important influences on a patient's responsiveness to  $\beta_2$ -adrenergic receptor ( $\beta_2$ -AR) agonists (such as albuterol). A single nucleotide polymorphism (SNP) at amino acid position 16 of the  $\beta_2$ -AR gene is the most common polymorphism and has been shown to be the most functionally relevant. A change at base 46 from adenine to guanine results in the amino acid sequence of the  $\beta_2$ -AR containing a glycine (Gly), rather than an arginine (Arg), at amino acid position 16. Patients homozygous for Gly at this position (Gly/Gly) have been shown to have improved responsiveness to  $\beta_2$ -AR agonist therapy when compared to children homozygous for Arginine (Arg/Arg) or heterozygous (Arg/Gly). Previous work has shown that bronchodilator responses in bronchiolitis range from marked improvement to actual deterioration of lung function. One reason for the inconsistency of these findings is the lack of sufficiently sensitive methods for evaluation of lung function in infants. In addition, grouped mean responses can fail to show individual variation in responsiveness. For example, a recent study demonstrated that post-albuterol bronchodilator measurements did not differ significantly from baseline measurements in an entire group of infants aged 2-18 months with bronchiolitis; however, 11 of the 41 patients (27%) showed significant increases in lung function following inhalation of 200 mcg albuterol via metered dose inhaler. We believe that genetic factors influence responsiveness to albuterol therapy in children with bronchiolitis. Specifically, we believe that  $\beta_2$ -AR polymorphisms at amino acid position 16 affect responsiveness to acute  $\beta_2$ -AR agonist therapy in children with bronchiolitis. In support of this concept, Moore et al recently demonstrated that RSV infection did not influence isoproterenol-induced cAMP formation in tracheal smooth muscle cells obtained from 2 donors homozygous for the Gly16 haplotype, but it significantly decreased isoproterenol-induced cAMP formation in cells from 2 individuals homozygous for the Arg16 haplotype. Thus, our hypothesis is that: children with bronchiolitis who are homozygous for glycine at amino acid position 16 (Gly/Gly) will have improved responses to albuterol therapy. We propose to investigate this research question in a prospective observational trial. Children admitted to the ICU with bronchiolitis, who are intubated and mechanically ventilated with a cuffed endotracheal tube and who are receiving albuterol will be included. Measurement of pulmonary function will be recorded before and after the albuterol from values routinely determined by the Servo-I ventilator in use in the Pediatric ICU at CCMC. Genotyping of the  $\beta_2$ -AR gene will be performed at the General Clinical Research Center at the University of Connecticut Health Center. Genotyping will be performed from whole blood that is added onto routine blood sampling. Children will be stratified based on their genotype and outcomes compared. Providers will be blinded to genotype at the time of treatment.

**SUBPROJECT PROGRESS:**

Bronchiolitis is a significant cause of morbidity and hospitalization in children, accounting for approximately 125,000 hospitalizations per year in the U.S. Recently, genetic variations of the  $\beta_2$ -adrenergic receptor ( $\beta_2$ -AR) have been shown to influence responsiveness to  $\beta_2$ -AR agonist therapy in children with asthma. We suspect that genetic variations of the  $\beta_2$ -AR also affect response to  $\beta_2$ -AR agonist therapy in children with bronchiolitis. Our hypothesis is that mechanically ventilated children with bronchiolitis who are homozygous for glycine at amino acid position 16 (Gly/Gly) will have improved pulmonary resistance following  $\beta_2$ -AR agonist therapy than children who are homozygous for arginine or heterozygous at amino acid position 16.

This project was approved on December 3, 2007 and began enrollment in December 15, 2007. Since that time, we have enrolled 15 of a planned 50 children in this trial. Genotyping of the  $\beta_2$ -AR gene was performed by the core laboratory of the GCRC. The core laboratory was able to genotype all samples provided. However, due to the small numbers of patients enrolled, interim data/statistical analysis has not been performed at this time.

There have been no safety concerns with this study. Nor are there any proposed changes or anticipated changes in the protocol or in the recruitment plans. There have been no publications or abstracts submitted for this study.

<b>SPID:</b> 0668	<b>PROTOCOL:</b> 668	<b>TYPE:</b> RESEARCH
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<b>SHORT TITLE:</b>	Smoking in Substance Abusers
<b>LONG TITLE:</b>	Contingency Management in Substance Abusers

AIDS:	N	TOTALS	A	B	D
			Inpatient	0	0
<b>START DATE:</b>	12/20/2007	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	Y	CLINICAL TRIAL	N
BIostatistician	N	CORE LAB	N
ANCILLARIES ONLY	N		

INVESTIGATOR	DEPARTMENT	NON-HOST INSTITUTION: STATE, COUNTRY
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ALESSI, SHEILA PHD	Psychiatry	
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#### SUBPROJECT DESCRIPTION:

Cigarette smoking, the most common source of preventable morbidity and mortality in the United States, is more prevalent and has more serious adverse health consequences in substance abusers compared to the general population. Contingency management (CM), in which tangible incentives are provided contingent on a target behavior like abstinence, is highly efficacious in improving substance abuse treatment outcomes and may be a useful smoking cessation tool in this difficult population. We have preliminary data suggesting the efficacy of CM for smoking abstinence. In this application, we propose a larger study to more rigorously evaluate a prize-based CM procedure for initiating smoking abstinence in residential substance abuse treatment patients who want to quit smoking. Patients (N=102) who meet diagnostic criteria for alcohol, cocaine, marijuana, or opiate abuse or dependence will meet with research staff on two days for quit preparation sessions (2 per day). These sessions include testing a breath sample for evidence of smoking twice each day (separated by at least 5 hours), counseling based on Public Health Service (PHS) guidelines for quitting smoking during the second session each day, and setting a quit date. After these sessions, participants will be randomly assigned to: (a) standard care or (b) standard care plus prize CM for smoking abstinence with the opportunity to win prizes (\$1-\$100 in value) for submitting samples that meet smoking abstinence criteria (e.g., CO  $\dot{U}$  6ppm; cotinine  $\dot{U}$  30ng/mL). Nicotine withdrawal, urges to smoke, depressive symptoms, and other (non-nicotine) substance use will be assessed weekly. In addition, self-efficacy, motivation to change, substance use, psychosocial problems, and depressive symptoms will be assessed at intake and 1, 2, 3 and 6 months following the quit date. Primary outcomes will be smoking abstinence based on CO and cotinine test results. Mediation effects of self-efficacy and motivation to change on outcomes will be tested. Participant characteristics that may be associated with improved outcomes within and across conditions will also be assessed. It is hypothesized that smoking abstinence rates will be higher in the CM condition compared to the standard care condition.

#### SUBPROJECT PROGRESS:

Total Enrollment: 0

Past Year Enrollment: 0

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 the following sentence to the Informed Consent Form (ICF), "You will receive a \$1 gift certificate each time samples are submitted at Quit Preparations sessions and study sessions during weeks 1-4 for a total of up to \$44" as stated in the Compensation section (page 5) in order to introduce the concept earlier in the document. 2) Revised the order of the sentence on page 3, first paragraph of the ICF under Treatment B to enhance comprehension. 3) Deleted the mention of McDonald's gift certificates in the ICF as McDonald's \$1 gift certificates may not be available for our purchase in the near future. 4) Clarified on page 9 of the protocol that the Mini-Mental State Exam is administered at intake as deemed necessary by the research assistant. 5) Revised the Patient Information Form, by removing questions related to cigarette smoking. The Patient Information Form will continue to be administered at baseline only. The cigarette smoking questions have been incorporated into a more extensive questionnaire called the Cigarette Smoking History Questionnaire that we administer at baseline and each follow-up interview. 6) Revised the Addiction Severity Index (ASI) adding questions regarding HIV status and previous/current treatment history questions. 7) Clarified in the protocol that questions related to gender, ethnicity and other demographic information is incorporated into the ASI. 8) Replaced the Beck Depression Inventory-II (BDI-II) with the Center for Epidemiological Studies-

Depressed Mood scale. 9) Added the Ways of Coping Checklist-Revised

Results not yet published as study is ongoing.

Do you wish to continue to receive GCRC resources for the period April 1, 2008 through March 31, 2009? Yes

<b>SPID:</b>	0670	<b>PROTOCOL:</b>	670	<b>TYPE:</b>	RESEARCH	
<b>SHORT TITLE:</b>	Exercise for Smoking					
<b>LONG TITLE:</b>	Exercise for Smoking Cessation in Postmenopausal Women					
<b>AIDS:</b>	N	<b>TOTALS</b>		<b>A</b>	<b>B</b>	<b>D</b>
		Inpatient		0	0	0
<b>START DATE:</b>	1/31/2008	Scatter Bed		0	0	0
Total # pts expected for entire study:	8	Outpatient		7	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
ONCKEN, CHERYL MD	Medicine	
KRANZLER, HENRY MD	Psychiatry	

#### SUBPROJECT DESCRIPTION:

Thirty percent of female smokers are postmenopausal, and this proportion is expected to grow as the population ages. Based on the elevated risk of osteoporosis in postmenopausal smokers, together with the high prevalence of depression history and considerable weight gain we observed in previous studies, we have chosen to examine the potential utility of exercise as an adjunct treatment for smoking cessation in postmenopausal women. The specific research aims of this study are to: 1)to evaluate whether adding an established moderate resistance/aerobic exercise program for postmenopausal women 50 years of age and older to a standard smoking cessation treatment program improves short and long term smoking outcomes; 2)to examine the main and interactive effects of history of depression and exercise on smoking cessation treatment; 3)to use interactive voice recording (IVR) technology to examine the mechanisms by which exercise may improve smoking treatment outcomes in postmenopausal women; 4)to examine whether adding a moderate exercise program to a standard smoking cessation treatment program for postmenopausal women improves health outcomes such as, weight gain, bone mineral density, and quality of life measurements. Study sites will include The University of Connecticut Health Center and the University of Minnesota. Subjects (N=364) must be postmenopausal, at least 50 years of age, and smoke at least 10 cigarettes per day. All subjects will receive smoking treatment (behavioral counseling and varenicline) and will be randomly assigned to either 1)a supervised exercise program or 2)a supervised relaxation control condition. We hypothesize that 1)postmenopausal women randomized to the exercise condition will have greater end of treatment abstinence rates and end of year abstinence rates than will those women assigned to an attention control condition. 2a)women with a history of depression will have reduced short and long-term smoking abstinence rates. b)ameliorative effects of exercise on smoking cessation and depression will exist such that women with a history of depression will abstain from smoking at a rate equivalent to those with no such history; 3)exercise may improve smoking cessation by reducing nicotine withdrawal symptoms and negative affect, and by increasing self-efficacy for smoking cessation; 4)women randomized to the exercise condition will have increased bone mineral density at the hip, and improved quality of life compared to women in the control condition. An effective exercise program added to smoking cessation for postmenopausal women has the potential to address many health problems in this at-risk population, and markedly improve quality of life.

#### SUBPROJECT PROGRESS:

7 subjects were enrolled (signed consent), 6 randomized to RX.  
 1 subject dropped out after screening. Time limitations too much  
 1 subject dropped out after 1 class due to a number of reasons (didn't like group setting, interfered with work, unable to tolerate any meds for smoking cessation)  
 1 subject dropped out after 2nd session declining to participate further  
 1 subject moved  
 3 subjects remain in treatment (10 out of 12 weeks). All have remained abstinent.

Our revised proposal is only a 12 week study. We are planning on submitting for approval for longer term follow-up on pilot subjects.

We are applying for funding, will only enroll a limited number of subjects to obtain feasibility data. We are considering one more

group session to enroll a few more participants.

<b>SPID:</b>	0676	<b>PROTOCOL:</b>	676	<b>TYPE:</b>	RESEARCH	
<b>SHORT TITLE:</b>	Contingency Management Treatment					
<b>LONG TITLE:</b>	Contingency Management Treatment 12 vs 24 Week Duration					
<b>AIDS:</b>	N	<b>TOTALS</b>		<b>A</b>	<b>B</b>	<b>D</b>
		Inpatient		0	0	0
<b>START DATE:</b>	2/21/2008	Scatter Bed		0	0	0
Total # pts expected for entire study:	310	Outpatient		0	0	0
		Scatter RN Hours		0	0	0
		Offsite Visits		5	0	0
<b>RESEARCH BIONUTRITION</b>	N	<b>MULTICENTER STUDY</b>		N		
<b>INFORMATICS CORE</b>	Y	<b>CLINICAL TRIAL</b>		N		
<b>BIostatistician</b>	N	<b>CORE LAB</b>		N		
<b>ANCILLARIES ONLY</b>	N					

<b>INVESTIGATOR</b>	<b>DEPARTMENT</b>	<b>NON-HOST INSTITUTION: STATE, COUNTRY</b>
PETRY, NANCY PHD	Psychiatry	

#### SUBPROJECT DESCRIPTION:

Contingency management (CM) interventions are highly efficacious in improving substance abuse treatment outcomes, but few studies have implemented this approach with alcohol use disorder patients. Further, no known studies have experimentally evaluated how duration of CM affects outcomes. This issue appears to be of central importance for impacting long-term behavior change, given the well-established association between length of treatment engagement and outcomes. In this application, we propose to evaluate the efficacy of prize-based CM when administered according to a usual duration of 12 weeks versus an extended duration of 24 weeks. We will also investigate how probabilities of reinforcement may impact the relationships between CM duration and outcomes. Alcohol abusing or dependent patients (N=310) beginning intensive outpatient day treatment at community based clinics will be randomly assigned to one of four conditions: (a) standard treatment as usual (ST) at the clinic without CM; (b) ST with CM for 12 weeks with a 0.5 probability of winning prizes for each negative sample submitted and an expected average maximum earnings of \$300 in prizes; (c) ST with CM for 24 weeks with a 0.34 probability of winning prizes for each negative sample submitted and an expected average maximum earnings of \$300 in prizes; or (d) ST with CM for 24 weeks with a 0.5 probability of winning prizes for each negative sample submitted and an expected average maximum earnings of \$500 in prizes. During weeks 1-12, two breath samples per week will be collected from all patients, and those in the CM conditions will have the opportunity to win prizes for submission of negative samples. Those assigned to the longer duration CM conditions will continue to receive reinforcement for negative samples provided weekly during weeks 13-24. In group d, probabilities of reinforcement will be identical to those used in group b, but they will remain available for an additional 12 weeks. In group c, the probabilities of winning prizes will be lower so that the magnitude of overall reinforcement is consistent with group b. Alcohol use, other drug use, psychosocial problems, and HIV risk behaviors will be measured at baseline, during and post treatment, and throughout an 18-month follow-up period. We expect that CM will decrease alcohol use to a greater extent than non-CM treatment, and that availability of CM for 24 weeks may result in longer term benefits than 12 week exposure to CM. This study will be the first to evaluate the effects of probability of winning prizes on response to CM. We will also assess patient characteristics that may be associated with improved outcomes within and across treatments

#### SUBPROJECT PROGRESS:

Total Enrollment: 2

Past Year Enrollment: 2

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 Danielle Barry as Study Coordinator and removed Sheila Alessi as Study Coordinator. 2) Clarified that the Demos referred to in the Assessment table in protocol are included in the ASI questionnaire. 3) Replaced the University of Rhode Island Change Assessment (URICA) with the Readiness to Change Questionnaire (RTCQ). 4) Added two new questionnaires: Alcohol Abstinence Self-Efficacy (AASE) scale to assess self-efficacy and the Coping Strategies Scale (CSS) to evaluate coping skills. 5) Clarified that the urine tests for stimulants, opiates, and marijuana will be performed using cups rather than sticks. 6) Expanded the description of the payment for urine samples submitted to include other small items up to \$2 in value (e.g., toiletries, snacks, bus tokens, etc.) in addition to gift certificates. 7) Specified in both the ICF and protocol that the random breath testing may be administered as needed one or more times during the 24-week treatment phase. 8) Corrected several typographical errors discovered in the protocol and ICF. 9) Removed two items from our 10-item Consent Quiz in order to match

the description of the 8-item Quiz in the protocol. 10) Updated HIPAA form to the IRB template. 11) Added questions to the Addiction Severity Index (ASI) regarding HIV status and previous and current treatment. 12) Clarified in the protocol that the DSM Checklist for stimulants includes cocaine, amphetamine and methamphetamine. 13) Clarified in the protocol amphetamine and methamphetamine, in addition to cocaine, will be recorded in the Timeline Follow-back (TLFB). 14) Revised version of the Cigarette Smoking History questionnaire and to clarify that it will be administered at intake and at each follow-up. 15) Added the following sentence to the ICF, "The breath sample will test for alcohol" in order to introduce the concept of testing breath samples for alcohol earlier in the document. 16) Added the name of one of the co-investigators, Danielle Barry to the audiotaping portion of the consent on page 6 of the ICF. 17) Revised Consent Quiz for enhanced comprehension.

- Results not yet published as study is ongoing.

Do you wish to continue to receive GCRC resources for the period April 1, 2008 through

March 31, 2009? Yes



**PUBLICATIONS: JOURNALS**

+Authored by CAP/MCAP, \*CRC Personnel

<b>SPIDs PMID Published</b>	<b>Cited</b>	<b>Reference</b>
0554 17400520	Y	+Abu-Hasaballah K, James A, Aseltine RH Jr. Lessons and pitfalls of interactive voice response in medical research. <i>Contemp Clin Trials</i> . 2007 Sep;28(5):593-602. Epub 2007 Mar 3.
0554 17870206	N	Academic ED SBIRT Research Collaborative The impact of screening, brief intervention, and referral for treatment on emergency department patients' alcohol use. <i>Ann Emerg Med</i> 50 699-710, 710.e1-6 2007.
0051 17942244	N	Agrawal A, Hinrichs AL, Dunn G, Bertelsen S, Dick DM, Saccone SF, Saccone NL, Grucza RA, Wang JC, Cloninger CR, Edenberg HJ, Foroud T, Hesselbrock V, Kramer J, Bucholz KK, Kuperman S, Nurnberger JI, Porjesz B, Schuckit MA, Goate AM, Bierut LJ Linkage scan for quantitative traits identifies new regions of interest for substance dependence in the Collaborative Study on the Genetics of Alcoholism (COGA) sample. <i>Drug Alcohol Depend</i> 93 12-20 2008.
0494 18385788	Y	Aragon-Martin JA, Ritch R, Liebmann J, O'Brien C, Blaaoow K, Mercieca F, Spiteri A, Cobb CJ, Damji KF, Tarkkanen A, Rezaie T, Child AH, Sarfarazi M. Evaluation of LOXL1 gene polymorphisms in exfoliation syndrome and exfoliation glaucoma. <i>Mol Vis</i> . 2008 Mar 17;14:533-41.
0605 17852005	Y	Barta WD, Kiene SM, Tennen H, Abu-Hasaballah KS, Ferrer R The idiographic study of inconsistent condom use behavior of persons living with HIV. <i>AIDS Care</i> 19 1058-64 2007.
0605 18071894	Y	Barta WD, Portnoy DB, Kiene SM, Tennen H, Abu-Hasaballah KS, Ferrer R A Daily Process Investigation of Alcohol-involved Sexual Risk Behavior Among Economically Disadvantaged Problem Drinkers Living with HIV/AIDS. <i>AIDS Behav</i> 2007.
0220 18226846	Y	Bauer LO A family history of psychopathology modifies the decrement in cognitive control among patients with HIV/AIDS. <i>Brain Cogn</i> 67 103-14 2008.
0220 18065165	Y	Bauer LO The effects of HIV on P300 are moderated by familial risk for substance dependence: implications for a theory of brain reserve. <i>Drug Alcohol Depend</i> 94 92-100 2008.
0468 17949392	Y	Bauer LO, Covault J, Harel O, Das S, Gelernter J, Anton R, Kranzler HR. Variation in GABRA2 predicts drinking behavior in project MATCH subjects. <i>Alcohol Clin Exp Res</i> . 2007 Nov;31(11):1780-7.
0554 18077305	Y	Bernstein E, Bernstein J, Feldman J, Fernandez W, Hagan M, Mitchell P, Safi C, Woolard R, Mello M, Baird J, Lee C, Bazargan-Hejazi S, Broderick K, Laperrier KA, Kellermann A, Wald MM, Taylor RE, Walton K, Grant-Ervin M, Rollinson D, Edwards D, Chan T, Davis D, Buchanan Marshall J, Aseltine R, James A, Schilling E, Abu-Hasaballah K, Baumann BM, Boudreaux ED, Maio RF, Cunningham RM, Murrell T, Doezema D, Anglin D, Eliassen A, Martin M, Pines J, Buchanan L, Turner J, D'Onofrio G, Degutis LC, Owens P An evidence based alcohol screening, brief intervention and referral to treatment (SBIRT) curriculum for emergency department (ED) providers improves skills and utilization. <i>Subst Abus</i> 28 79-92 2007.
0514 18194227	Y	+Boxer RS, Dauser DA, Walsh SJ, Hager WD, Kenny AM. The association between vitamin D and inflammation with the 6-minute walk and frailty in patients with heart failure. <i>J Am Geriatr Soc</i> . 2008 Mar;56(3):454-61. Epub 2008 Jan 5.
0514 18174754	Y	+Boxer RS, Wang Z, Walsh SJ, Hager D, Kenny AM. The utility of the 6-minute walk test as a measure of frailty in older adults with heart failure. <i>Am J Geriatr Cardiol</i> . 2008 Jan-Feb;17(1):7-12.
0563 17560739	N	Brumback T, Cao D, King A. Effects of alcohol on psychomotor performance and perceived impairment in heavy binge social drinkers. <i>Drug Alcohol Depend</i> . 2007 Nov 2;91(1):10-7. Epub 2007 Jun 8.
0468 17507911	Y	+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. <i>Neuropsychopharmacology</i> . 2008 Mar;33(4):837-48. Epub 2007 May 16.
0560 16920076	Y	Covault J, Tennen H, Armeli S, Conner TS, Herman AI, Cillessen AH, Kranzler HR Interactive effects of the serotonin transporter 5-HTTLPR polymorphism and stressful life events on college student drinking and drug use. <i>Biol Psychiatry</i> 61 609-16 2007.
0292 17938216	Y	Cruz AR, Moore MW, La Vake CJ, Eggers CH, Salazar JC, Radolf JD Phagocytosis of <i>Borrelia burgdorferi</i> , the Lyme disease spirochete, potentiates innate immune activation and induces apoptosis in human monocytes. <i>Infect Immun</i> 76 56-70 2008.
0297 17595258	Y	+Davenport ML, Crowe BJ, Travers SH, Rubin K, Ross JL, Fechner PY, Gunther DF, Liu C, Geffner ME, Thrailkill K, Huseman C, Zagar AJ, Quigley CA. Growth hormone treatment of early growth failure in toddlers with Turner syndrome: a randomized, controlled, multicenter trial. <i>J Clin Endocrinol Metab</i> . 2007 Sep;92(9):3406-16. Epub 2007 Jun 26.
0051 18316677	N	Dick DM, Aliev F, Wang JC, Grucza RA, Schuckit M, Kuperman S, Kramer J, Hinrichs A, Bertelsen S, Budde JP, Hesselbrock V, Porjesz B, Edenberg HJ, Bierut LJ, Goate A Using dimensional models of externalizing psychopathology to aid in gene identification. <i>Arch Gen Psychiatry</i> 65 310-8 2008.

0051 18163977	N	Dick DM, Aliev F, Wang JC, Saccone S, Hinrichs A, Bertelsen S, Budde J, Saccone N, Foroud T, Nurnberger J, Xuei X, Conneally PM, Schuckit M, Almasy L, Crowe R, Kuperman S, Kramer J, Tischfield JA, Hesselbrock V, Edenberg HJ, Porjesz B, Rice JP, Bierut L, Goate A A Systematic single nucleotide polymorphism screen to fine-map alcohol dependence genes on chromosome 7 identifies association with a novel susceptibility gene ACN9. <i>Biol Psychiatry</i> 63 1047-53 2008.
0421,0482 17328657	Y	Dieckhaus KD, Odesina V Outcomes of a multifaceted medication adherence intervention for HIV-positive patients. <i>AIDS Patient Care STDS</i> 21 81-91 2007.
0051 18079108	N	Edenberg HJ, Xuei X, Wetherill LF, Bierut L, Bucholz K, Dick DM, Hesselbrock V, Kuperman S, Porjesz B, Schuckit MA, Tischfield JA, Almasy LA, Nurnberger JI, Foroud T Association of NFKB1, which encodes a subunit of the transcription factor NF-kappaB, with alcohol dependence. <i>Hum Mol Genet</i> 17 963-70 2008.
0496 17914043	N	Feder HM, Johnson BJ, O'Connell S, Shapiro ED, Steere AC, Wormser GP, Ad Hoc International Lyme Disease Group, Agger WA, Artsob H, Auwaerter P, Dumler JS, Bakken JS, Bockenstedt LK, Green J, Dattwyler RJ, Munoz J, Nadelman RB, Schwartz I, Draper T, McSweeney E, Halperin JJ, Klempner MS, Krause PJ, Mead P, Morshed M, Porwancher R, Radolf JD, Smith RP, Sood S, Weinstein A, Wong SJ, Zemel L A critical appraisal of "chronic Lyme disease". <i>N Engl J Med</i> 357 1422-30 2007.
0442 18175357	Y	Fontana RJ, Goodman ZD, Dienstag JL, Bonkovsky HL, Naishadham D, Sterling RK, Su GL, Ghosh M, Wright EC, HALT-C Trial Group Relationship of serum fibrosis markers with liver fibrosis stage and collagen content in patients with advanced chronic hepatitis C. <i>Hepatology</i> 47 789-98 2008.
0478, 0533 17362299	Y	Ghaziani T, Alavian SM, Zali MR, Shahraz S, Agah M, Jensen KP, Ansari S, Sendi H, Lambrecht RW, Covault J, Bonkovsky HL Serum measures of iron status and HFE gene mutations in patients with hepatitis B virus infection. <i>Hepatol Res</i> 37 172-8 2007.
0051 18454434	N	Ghosh S, Bierut LJ, Porjesz B, Edenberg HJ, Dick D, Goate A, Hesselbrock V, Nurnberger J, Foroud T, Kramer J, Rice J, Begleiter H A novel non-parametric regression reveals linkage on chromosome 4 for the number of externalizing symptoms in sib-pairs. <i>Am J Med Genet B Neuropsychiatr Genet</i> 2008.
0596 18263592	Y	Grover R, Frank ME Regional specificity of chlorhexidine effects on taste perception. <i>Chem Senses</i> 33 311-8 2008.
0560 17942837	Y	Gunthert KC, Conner TS, Armeli S, Tennen H, Covault J, Kranzler HR. Serotonin transporter gene polymorphism (5-HTTLPR) and anxiety reactivity in daily life: a daily process approach to gene-environment interaction. <i>Psychosom Med</i> . 2007 Nov;69(8):762-8. Epub 2007 Oct 17.
0658, 0325 18550918	Y	+Hegde U, Chhabra A, Chattopadhyay S, Das R, Ray S, Chakraborty NG. Presence of low dose of fludarabine in cultures blocks regulatory T cell expansion and maintains tumor-specific cytotoxic T lymphocyte activity generated with peripheral blood lymphocytes. <i>Pathobiology</i> . 2008;75(3):200-8.
0591 17942842	Y	Herbst S, Pietrzak RH, Wagner J, White WB, Petry NM. Lifetime major depression is associated with coronary heart disease in older adults: results from the National Epidemiologic Survey on Alcohol and Related Conditions. <i>Psychosom Med</i> . 2007 Nov;69(8):729-34. Epub 2007 Oct 17.
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0295 17661195	Y	Petry NM. Concurrent and predictive validity of the Addiction Severity Index in pathological gamblers. <i>Am J Addict</i> 16 272-82 2007.
0381 17956613	N	Reynolds JM, El Bissati K, Brandenburg J, Günzl A, Mamoun CB. Antimalarial activity of the anticancer and proteasome inhibitor bortezomib and its analog ZL3B. <i>BMC Clin Pharmacol</i> 7 13 2007.
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Genetic Variation in the CHRN5 Gene Affects mRNA Levels and is Associated with Risk for Alcohol  
Dependence *Molecular Psychiatry.*

**SOURCE OF INVESTIGATORS' SUPPORT****FOUNDATION**

<b>SOURCE</b>	<b>GRANT/CONTRACT</b>	<b>FUNDS</b>	<b>SPID</b>
ALBERTSEN, PETER			
CTRC RESEARCH FOUNDATION		12,210	0365
KENNY, ANNE			
DONAGHUE FOUNDATION		109,450	0624
DONAGHUE FOUNDATION		110,000	0614, 0617, 0648
MAYER, BRUCE			
UCONN FOUNDATION		2,114	0445, 0477
ONCKEN, CHERYL			
DONAGHUE FOUNDATION		123,734	0466, 0598
SARFARAZI, MANSOOR			
GLAUCOMA FOUNDATION		40,000	0494
	<b>FOUNDATION</b>	<b>\$397,508</b>	

**INDUSTRY**

<b>SOURCE</b>	<b>GRANT/CONTRACT</b>	<b>FUNDS</b>	<b>SPID</b>
LALLA, RAJESH			
i3 RESEARCH		3,014	0666
MIRZA, FARYAL			
AMGEN CENTER		43,980	0661
	<b>INDUSTRY</b>	<b>\$46,994</b>	

**PVAS**

<b>SOURCE</b>	<b>GRANT/CONTRACT</b>	<b>FUNDS</b>	<b>SPID</b>
PAPPAGALLO, MARIANN			
CHILDRENS HOSPITAL ASSOCIATION		2,646	0459
WAGNER, JULIE			
AMERICAN HEART ASSOCIATION		65,000	0591
	<b>PVAS</b>	<b>\$67,646</b>	

**SCC**

<b>SOURCE</b>	<b>GRANT/CONTRACT</b>	<b>FUNDS</b>	<b>SPID</b>
BAUER, LANCE			
DEPARTMENT OF PUBLIC HEALTH		538,605	0660
	<b>SCC</b>	<b>\$538,605</b>	

**OTHER NON FEDERAL**

<b>SOURCE</b>	<b>GRANT/CONTRACT</b>	<b>FUNDS</b>	<b>SPID</b>
ABU-HASABALLAH, KHAMIS			
YALE UNIVERSITY		2,448	0622
BENMAMOUN, CHOUKRI			
OREGON HEALTH & SCIENCE		132,163	0587
UNIVERSITY			
BONA, ROBERT			
UNIV OF PITTSBURGH		1,700	0659
CHERNIACK, MARTIN			
UMASS LOWELL		380,139	0643
CLOUTIER, MICHELLE			
CT CHILDREN'S MEDICAL CENTER		50,079	0626
CT CHILDREN'S MEDICAL CENTER		139,389	0626
HESSELBROCK, VICTOR			
AMERICAN COLLEGE OF		9,999	0637
GASTROENTEROLOGY			

SUNY - BROOKLYN	33,795	0051
SUNY - BROOKLYN	655,041	0051
KENNY, ANNE YALE UNIVERSITY	203,102	0645
KRANZLER, HENRY YALE UNIVERSITY	236,909	0357
KURTZMAN, SCOTT UNIV OF PITTSBURGH	20,050	0290
UNIV OF PITTSBURGH	33,370	0279, 0282, 0286, 0329, 0372, 0399, 0400, 0428, 0506, 0575, 0576, 0577, 0578
PETRY, NANCY YALE UNIVERSITY	125,632	0519, 0548, 0613, 0623
YALE UNIVERSITY	417,728	0519, 0548, 0613, 0623
SALAZAR, JUAN CT CHILDREN'S MEDICAL CENTER	76,754	0651
CT CHILDREN'S MEDICAL CENTER	32,400	0651
CT CHILDREN'S MEDICAL CENTER	76,754	0651
UMASS	72,179	0500, 0642
TANNENBAUM, SUSAN TUFTS NEW ENGLAND MEDICAL CENTER	13,818	0641
WAGNER, JULIE BOYS & GIRLS VILLAGE	100,000	0453

**OTHER NON FEDERAL****\$2,813,449****FEDERAL**

SOURCE	GRANT/CONTRACT	FUNDS	SPID
<b>Federal - PHS</b>			
ALESSI, SHEILA NIH	1R21DA021836-01A2	220,560	0668
BAUER, LANCE NIH	5R01DA017666-03	323,203	0599
BONKOVSKY, HERBERT NIH	5U01DK065193-04	174,000	0551, 0562
CLOUTIER, MICHELLE NIH	5R01HL070785-05	662,013	0626
COVAULT, JONATHAN NIH	5R01AA015606-02	411,122	0620
NIH	1R21AA017584-01	296,486	0630
CRANFORD, JAMES NIH	5R21AA015105-02	175,265	0636
DONGARI-BAGTZOGLOU, ANNA NIH	5R01DE013986-06	318,584	0526, 0572
FORD, JULIAN NIH	5K23MH001889-05	175,694	0618
FRANK, MARION NIH	5R01DC004099-07	421,066	0596
NIH	5R01DC004849-05	267,137	0596
NIH	3R01DC004099-06A2S	14,500	0596
FREILICH, MARTIN A	1		

NIH	5R01DE017873-02	537,235	0638
GELERNTER, JOEL			
NIH	5R01DA012690-08	1,062,418	0357
NIH	5R01AA011330-08	705,574	0599
HESSELBROCK, VICTOR			
NIH	5P50AA003510-30	1,706,726	0051
NIH	2P60AA003510-31	1,799,998	0051
KADDEN, RONALD M			
NIH	5R01DA012728-07	522,689	0364
KRANZLER, HENRY			
NIH	5K24AA013736-05	135,778	0468, 0536, 0665
NIH	5R01AA013631-05	256,591	0531
NIH	5R01DA018432-02	766,884	0340
LALLA, RAJESH			
NIH	5K23DE016946-03	132,324	0487
LITT, MARK			
NIH	5R01DE014607-05	302,248	0497
NIH	5R21AA014202-03	140,331	0589
MAYER, BRUCE			
NIH	5R01CA082258-09	309,344	0445, 0477
MCELHANEY, JANET			
NIH	5R01AI068265-07	413,917	0524
MEYER, JOHN			
CDC	5R21OH008543-02	179,450	0590
MUKHERJI, BIJAY			
NIH	5R01CA117254-03	255,082	0658
ONCKEN, CHERYL			
NIH	5R01DA015167-05	274,632	0466
PACHTER, LEE			
NIH	5K23HD040348-05	107,488	0632
PETRY, NANCY			
NIH	5R01DA018883-04	416,283	0519
PROTIVA, PETR			
NIH	5U01DK065193-05	225,793	0551, 0562
RADOLF, JUSTIN			
NIH	2R01AI026756-20A1	480,083	0292
REICHENBERGER, ERNST			
NIH	2R01AR045286-06A1	442,729	0492, 0518
SALAZAR, JUAN			
NIH	1R03TW008023-01	39,380	0651
NIH	5K23AI062439-03	150,820	0651
SARFARAZI, MANSOOR			
NIH	5R01EY014959-04	316,800	0494
NIH	5R01EY011095-12	516,117	0494
SULLIVAN, TAMI			
NIH	5K23DA019561-03	180,223	0622
WAGNER, JULIE			
NIH	1R21DK074468-01A2	222,000	0664
WOLFSON, LESLIE			
NIH	5R01AG022092-04	586,274	0582

Federal - PHS

\$16,644,841

FEDERAL

\$16,644,841

TOTAL FUNDING:

\$20,509,043

**RESOURCE SUMMARY: SUBPROJECTS**

The following only includes information associated with subprojects.

	<b>Pilot (CReFF)</b>	<b>Research</b>	<b>Core Inf.</b>	<b>Total</b>
Number of Subprojects	0	151	0	151
Number of Investigators	0	199	0	199
Number of Published	0	56	0	56
Number of In Press	0	6	0	6
<b>Subprojects Using</b>	<b>A</b>	<b>B</b>	<b>D</b>	
Inpatient Days	0	0	0	
Scatter Bed Days	0	0	0	
Outpatient Visits	5,992	284	0	
Scatter RN Hours	0	0	0	
Offsite Research Visits	4,410	0	0	
<b>Subprojects Using</b>	<b>Total SPID Count</b>			
Patient Days/Visits	82			
Research Bionutrition	0			
Informatics Core	151			
Biostatistician	9			
Ancillaries Only	0			
Multicenter	40			
Clinical Trial	26			
Core Lab	62			



**RESOURCE SUMMARY: ADMINISTRATIVE****GCRC Personnel Function**

Program Direction	0.410
Administration	1.600
Nutrition and dietary support	0.000
Bioinformatics, computer systems managers	1.400
Biostatistician	0.530
Nursing	7.600
Research Subproject Advocacy	1.200
Core lab staff	3.850
Other	0.900
Total FTEs:	17.490

**INVESTIGATORS****On Subprojects****Not On Subprojects**

Clinical Investigators	199	11
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**GEOGRAPHICAL USAGE BY INVESTIGATORS AT NON-HOST INSTITUTIONS**

<b>Subproject Investigators by Country</b>	<b>1</b>
CANADA	1
<b>USA Subproject Investigators by State</b>	<b>53</b>
CT	39
DC	4
IL	2
MA	4
MI	1
NC	1
NY	2

**CLINICAL INVESTIGATORS BY DEGREE**

PHD Only	68
PHD and MD	8
PHD and Dental	1
PHD and Other Doctoral	0
MD Only	111
MD and Other Doctoral	0
Dental Only	11
Educator Only	0
Other Doctoral Only	1
NON-Doctoral ONLY	18
NO DEGREE	0

**RESOURCE SUMMARY: PUBLICATION/SUPPORT****PUBLICATIONS**

	Published		In Press	
	Cited	Total	Cited	Total
Journals	49	68	1	6

**INVESTIGATOR SUPPORT****NON-FEDERAL**

FOUNDATION	\$397,508
INDUSTRY	\$46,994
OTHER	\$2,813,449
PVAS	\$67,646
SCC	\$538,605

<b>NON-FEDERAL</b>	<b><u>3,864,202</u></b>
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**FEDERAL****PHS**

AA	\$5,627,871
AG	\$586,274
AI	\$1,044,820
AR	\$442,729
CA	\$564,426
CDC	\$179,450
DA	\$3,766,892
DC	\$702,703
DE	\$1,290,391
DK	\$621,793
EY	\$832,917
HD	\$107,488
HL	\$662,013
MH	\$175,694
TW	\$39,380

<b>PHS</b>	<b><u>16,644,841</u></b>
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<b>TOTAL SUPPORT</b>	<b><u><u>\$20,509,043</u></u></b>
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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	22	1	0
b. 1 thru 12 years	166	7	0
c. 13 thru 21 years	472	0	0
d. 22 thru 65 years	3,719	227	0
e. 66 and over	1,613	49	0
Total	5,992	284	0

**Age Census Offsite**

Age Group	OFFSITE RESEARCH VISITS	
	A	B
a. less than 1 year	1	0
b. 1 thru 12 years	210	0
c. 13 thru 21 years	217	0
d. 22 thru 65 years	3,969	0
e. 66 and over	13	0
Total	4,410	0



**Utilization Table**

Funding Category	INPATIENT		SCATTER BED		OUTPATIENT	
	Awarded	Used	Awarded	Used	Awarded	Used
A	0	0	0	0	0	5,992
B	0	0	0	0	0	284
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	5,221	276	0	0	4,410	0
b. >= 1 and <= 3	542	3	0	0	0	0
c. > 3 and <= 6	98	5	0	0	0	0
d. > 6 and <= 10	65	0	0	0	0	0
e. > 10 hours	66	0	0	0	0	0
Total	5,992	284	0	0	4,410	0

**GCRC Capacity****Number**

Total Inpatient Beds	0
Inpatient Beds Used for Outpatients	0
Outpatient Rooms	8

**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:				8/3/2006	
3.	Period applicable rate:	4/1/2007	through	6/30/2007		
4.A.	Routine Cost (or Space Cost for Per Diem Method):					0
4.B.	Per Diem Method:	0	Category A days x \$	790.04	=	0
4.C.	Scatter Beds:	0	Category A days x \$	790.04	=	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 Ancill					
	1,414	Category A Visits x \$	3.24	=	4,575.95	
	97	Category B Visits x \$	0.00	=	0.00	
	Total Outpatient Ancillaries					\$4,576
11.	Other Costs (Specify: drugs, raw food, special diets, outside laboratories, facility fees, etc. Provide justification)					\$29,373
12.	Outpatient Credits:					
	97	Category B Visits x \$	1.00	=	97	
	0	Category C Visits x \$	0.00	=	0	
	0	Category D Visits x \$	0.00	=	0	
12.A.	Total Outpatient Credits					\$97
12.B.	All Other Outpatient Credits (specify: grants, contracts, other sources)					\$0
	Total Credits (12A and 12B)					(\$97)
13.	Total Outpatient Charges (Lines 9, 10, and 11, less line 12)					\$33,852
14.	Total Ancillary Costs Connected with Ancillary-Only Projects					\$0
15.	Total Ancillary Costs Connected with Offsite Research Visits					\$0
	<b>TOTAL PATIENT CARE CHARGES (Lines 8 + 13 + 14)</b>					<b>\$33,852</b>

## 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:				3/6/2007	
3.	Period applicable rate:	7/1/2007	through	3/31/2008		
4.A.	Routine Cost (or Space Cost for Per Diem Method):					0
4.B.	Per Diem Method:	0	Category A days x \$	924.99	=	0
4.C.	Scatter Beds:	0	Category A days x \$	924.99	=	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 Ancill					
	4,578	Category A Visits x \$	10.46	=	47,888.30	
	187	Category B Visits x \$	0.00	=	0.00	
	Total Outpatient Ancillaries					\$47,888
11.	Other Costs (Specify: drugs, raw food, special diets, outside laboratories, facility fees, etc. Provide justification)					\$80,228
12.	Outpatient Credits:					
	187	Category B Visits x \$	1.00	=	187	
	0	Category C Visits x \$	0.00	=	0	
	0	Category D Visits x \$	0.00	=	0	
12.A.	Total Outpatient Credits					\$187
12.B.	All Other Outpatient Credits (specify: grants, contracts, other sources)					\$0
	Total Credits (12A and 12B)					(\$187)
13.	Total Outpatient Charges (Lines 9, 10, and 11, less line 12)					\$127,930
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)					\$127,930

4/1/2007 6/30/2007

**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>
Medica/Dental Supplies	0.00	9,057.95
Outside Labs	0.00	16,099.83
Patient Nutrition	0.00	408.01
Research Pharmacy	0.00	3,807.45
Grand Total:	0.00	29,373.24

7/1/2007 3/31/2008

**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>
Medical/Dental Supplies	0.00	24,740.37
Outside Labs	0.00	43,974.17
Patient Nutrition	0.00	1,114.43
Research Pharmacy	0.00	10,399.46
Grand Total:	0.00	80,228.43

## INPATIENT

1. If proposed rate is used, show date filed with HHS:
2. If rate has been published by HHS, show date of agreement: 8/3/2006
3. Period applicable rate: 04/01/2007 through 06/30/2007
- 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
 

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

9. Space Charge \$0
10. Outpatient Ancillaries Required Solely for Research Purposes, Adjusted to Cost (Schedule 2)
 

5,992	Category A Visits	52,464
284	Category B Visits	0

 Total Outpatient Ancillaries \$52,464



11.	Other Costs (Specify: drugs, raw food, special diets, outside laboratories, facility fees, etc. Provide justification)			\$109,602
12.	Outpatient Credits:			
	284	Category B Visits	284	
	0	Category C Visits	0	
	0	Category D Visits	0	
12.A.	Total Outpatient Credits			\$284
12.B.	All Other Outpatient Credits (specify: grants, contracts, other sources)			\$0
	Total Credits (12A and 12B)			\$(284)
13.	Total Outpatient Charges (Lines 9, 10, and 11, less line 12)			\$161,782
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)				\$161,782

**ANCILLARY CHARGES REQUIRED FOR RESEARCH PURPOSES****Department/ Cost Center****INPATIENT****Gross Charges****Adjustment  
Factor (%)****Net Charges**ABAB

TOTAL

**Department/ Cost Center****OUTPATIENT****Gross Charges****Adjustment  
Factor (%)****Net Charges**ABAB

Rate Period: 4/1/2007-6/30/2007

Clinical Lab

12,851.00

0.00

34.00%

4,369.34

0.00

Nuclear Medicine

296.00

0.00

69.80%

206.61

0.00

TOTAL

13,147.000.004,575.950.00

Rate Period: 7/1/2007-3/31/2008

Clinical Lab

64,568.49

0.00

38.40%

24,794.30

0.00

DXA

11,092.00

0.00

100.00%

11,092.00

0.00

Pathology

9,000.00

0.00

100.00%

9,000.00

0.00

Professional Fees

565.00

0.00

80.00%

452.00

0.00

Radiation Therapy

2,550.00

0.00

100.00%

2,550.00

0.00

TOTAL

87,775.490.0047,888.300.00

**CORE LABORATORY**

<b>Test Name</b>	<b># of Tests</b>	<b># of SPIDS</b>	<b>SPIDS</b>
25-OH Vitamin D	261	3	0609, 0624, 0614
Bone Specific Alkaline Phosphatase	135	1	0624
Cortisol	149	2	0590, 0497
Creatinine	78	1	0413
DNA Extraction	3,371	28	0602, 0637, 0665, 0646, 0628, 0630, 0582, 0657, 0660, 0611, 0612, 0619, 0599, 0340, 0357, 0471, 0478, 0495, 0492, 0494, 0413, 0518, 0461, 0231, 0453, 0531, 0466, 0468
Endothelin 1-21	108	1	0591
E-Selectin	27	1	0568
Estradiol	175	2	0624, 0542
Estrone	40	1	0542
Estrone Sulfate	40	1	0542
FACS Analysis	228	1	0624
Genotyping	33,397	9	0602, 0630, 0560, 0612, 0619, 0549, 0495, 0492, 0466
hsCRP	89	3	0641, 0653, 0591
IL-1 beta	102	2	0568, 0497
IL-10	75	1	0497
IL-2	75	1	0497
IL-4	75	1	0497
IL-6	137	3	0641, 0653, 0497
intact PTH	199	2	0624, 0614
Lyme Screening	260	1	0496
Nitric Oxide	108	1	0591
N-telopeptide Collagen Crosslinks	213	2	0624, 0413
Osteocalcin	135	1	0624
PBMC Isolation	296	2	0646, 0624
Processing	12,056	35	0637, 0601, 0638, 0641, 0644, 0645, 0624, 0661, 0628, 0664, 0562, 0653, 0582, 0591, 0659, 0660, 0611, 0619, 0599, 0365, 0487, 0496, 0497, 0413, 0426, 0461, 0051, 0442, 0528, 0268, 0529, 0453, 0535, 0466, 0542
RNA Extraction	73	3	0637, 0646, 0461
RT-PCR	513	2	0600, 0530
Sequencing	248	6	0637, 0625, 0612, 0549, 0492, 0530
SHBG	175	2	0624, 0542
Testosterone	79	1	0542
Thrombin/Anti-thrombin III complex	27	1	0568
Tissue Factor	27	1	0568
TNF alpha	108	3	0568, 0581, 0497
VEGF	27	1	0568

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## 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
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Current Appoint:

Current Address:

Phone Number:

## 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 a 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.

#### DOUGLAS, KARA R

Degree Sought	BS, BS
Mentor Name	KRANZLER, HENRY
Period	06/01/2007 - 08/31/2007
Funds Received	3,200 *
Project Title	Effects of Aripiprazole on Subjective Responses to Alcohol
SPIDS	0536, 0536
Project Summary	I assisted data cleaning and analysis for the following study and co-authored a manuscript, which is nearing readiness to be submitted for publication: Aripiprazole is of interest as a potential pharmacologic intervention for the treatment of alcoholism. This study included 18 healthy subjects who were assigned to receive a high, low, or no-med dosage of aripiprazole in a randomized, double-blind, within-subjects design. The subjects then completed an alcohol challenge lab during which vital signs were monitored and self-report surveys were used to measure subjective alcohol effects. It was found that the high dosage of aripiprazole significantly reduced the pleasurable and euphoric effects of alcohol consumption, while increasing feelings of sedation.

#### GRILLE, MICHAEL

Degree Sought	MD, BS
Mentor Name	PROTIVA, PETR
Period	06/01/2007 - 08/31/2007
Funds Received	3,200 *
Project Title	The Effect of Acute Aerobic Exercise on the Colorectal Mucosa
SPIDS	
Project Summary	An investigation of the possible mechanisms responsible for the observed risk reduction in colon cancer associated with aerobic exercise. The study focuses on several pathways with effects on apoptosis and cell cycle progression including IGF receptor-mediated signaling, PGE, and changes in gene expression.

#### KAPTUCH, JUSTIN

Degree Sought	MD, BS
Mentor Name	ONYIUIKE, HILARY
Period	06/01/2007 - 08/31/2007
Funds Received	3,200 *
Project Title	A retrospective review of cervical corpectomy in instrumented and non-instrumented fusions: indications, radiological features, complications, and outcomes
SPIDS	
Project Summary	This study examines the indications and outcomes of a surgery, cervical corpectomy, commonly performed to alleviate cervical spinal cord compression or cervical myelopathy.

#### KOZLAK, SCOTT

Degree Sought	DMD, BS
Mentor Name	LALLA, RAJESH
Period	06/01/2007 - 08/31/2007
Funds Received	3,200 *
Project Title	Vitamin Levels in Patients with RAS

SPIDS 0592, 0592  
 Project Summary Vitamin levels in patients with recurrent aphthous stomatitis (RAS) are measured using a diet history questionnaire and accompanying Diet-Calc software from the National Cancer Institute. These levels are compared to the levels found in a normal population to look for differences between the RAS cohort and the normal population.

**MADEJ, OLGA**

Degree Sought BA, MD  
 Mentor Name MENZOIAN, JAMES  
 Period 06/01/2007 - 08/31/2007  
 Funds Received 3,200 \*  
 Project Title Incidence and Risk Factors for Transient Hypotension Following Carotid Endarterectomy and Carotid Angioplasty with Stenting.

SPIDS  
 Project Summary I worked on a retrospective review of 500+ charts from 3 hospitals: John Dementsy, St. Francis, and Hartford. I collected demographic and pertinent medical history data from patients that underwent carotid surgery for the treatment of carotid artery occlusive disease. The purpose was to determine the incidence of transient hypotension after the procedures (at the 3 hospitals), and what, if any, risk factors exist.

**ROPER, NITIN**

Degree Sought MD, BS  
 Mentor Name FANG, MIN  
 Period 06/01/2007 - 08/31/2007  
 Funds Received 3,200 \*  
 Project Title Pharmacogenetics of Warfarin Therapy

SPIDS 0662, 0662  
 Project Summary Coumadin (warfarin) is a blood thinner to help prevent serious and even fatal blood clots. However, it is not easy to determine the correct dose. If a patient does not take enough Coumadin, blood clots can form and if the dose given is too high, a person can have bleeding, which can be fatal. Some of the differences in individual dose needed to achieve therapeutic effect may be caused by the enzymes in an individual that break down the drug. Current dosing schedules, however, do not account for these genetic factors. Recent studies have shown strong evidence that individuals with certain genetic makeup require lower doses of Coumadin.

The purpose of this research study is to identify patient genetic factors that may allow for a lower dose of Coumadin to be used and to find a better way to determine the correct dose for every patient.

**WALSH, KEVIN**

Degree Sought BA, MD  
 Mentor Name MAYER, BRUCE  
 Period 06/01/2007 - 08/31/2007  
 Funds Received 3,200 \*  
 Project Title Determining the Role of Nck in Cellular Protrusion and Motility Stimulated by PDGF

SPIDS

## Project Summary

Membrane protrusion plays an important role in cell motility. Altered membrane protrusion and cell motility have been linked with many diseases including atherosclerosis, diabetic retinopathy, and cancer. The Nck1 and Nck2 adaptor proteins link tyrosine phosphorylation with cytoskeletal dynamics, however, the role Nck plays in controlling membrane protrusion downstream of the activated PDGFR has not been elucidated. In this study the cellular levels of the Nck1 or Nck2 adapter proteins in NIH3T3 cells were down regulated using siRNA, and the cells were imaged using DIC microscopy. The cells were imaged for 10 minutes under starvation conditions, and imaged for another 10 minutes following PDGF stimulation. The protrusion patterns were then examined using kymograph analysis. The average protrusion velocity was similar for control and Nck1 knockdown cells under starvation (0.0387  $\mu\text{m/s}$ ). PDGF stimulation resulted in increased protrusion velocity by 56% in control cells, and 7% in Nck1 knockdown cells. The average protrusion distance was also similar for control and Nck1 knockdown cells under starvation (1.36  $\mu\text{m}$ ). PDGF stimulation resulted in increased protrusion distance by 83% in control cells, and 26% in Nck1 knockdown cells. These results suggest Nck plays an important role in mediating cellular protrusion downstream of the activated PDGFR.

## ZAKKO, LIAM

Degree Sought MD, BA  
 Mentor Name SMILOWITZ, HENRY  
 Period 06/01/2007 - 08/31/2007  
 Funds Received 3,200 \*  
 Project Title Cellular Basis for the Efficacy of Uric Acid-Enhanced Immunotherapy for F-98 Rat Glioma

## SPIDS

## Project Summary

Experimental results have shown that the lifespan of Fischer 344 rats with intracranial implantation of F-98 malignant glioma was improved when followed by T regulatory cell depletion and weekly injections of Granulocyte Macrophage Stimulating Factor (GM-CSF) transfected and then irradiated F-98 cells (GVax). The improvement was even more marked when the weekly GVax injections were accompanied with a dose of uric acid. An attempt was therefore made to determine the cellular mechanism for the difference in outcomes between these treatment methods by looking for the differences in immune cell responses to F-98 tumor cells in vitro. Flow cytometry data indicated that lymphocytes from the rats with uric acid injections produced 3 fold more Interferon gamma (IFN-  $\gamma$ ) than untreated rats and about 40% more IFN-  $\gamma$  than rats treated with GVax without uric acid. Interestingly, however, about 30% of the IFN-  $\gamma$  produced did not come from T-cells, but from other lymphocytes.

The research this summer attempted to discover what other cells were producing IFN-  $\gamma$ . It was hypothesized that perhaps Natural Killer (NK) cells or Natural Killer like T (NKT) cells were responsible. To test this theory a number of Fischer 344 Rats were treated with Gvax and uric acid. Five days after treatment the rats' spleens were collected and lymphocytes were isolated. Fluorescent labeling of the lymphocytes after this extraction, followed by flow cytometry, revealed a number of cell populations: some cells were  $\alpha\alpha\text{TCR}^+$  indicating they were T-cells; other cells were  $\text{CD161}^+$  indicating they were NK cells; still other cells were  $\alpha\alpha\text{TCR}^+$  and  $\text{CD 161}^+$  indicating they were NKT cells. Performing the same experiment except incubating the lymphocytes overnight in cell growth medium revealed the same populations. Repeating the experiment, however, with the lymphocytes incubated overnight in the presence of F-98 cells appeared to cause the loss of  $\text{CD 161}^+$  cell populations. Experiments showed that the loss of these populations occurred over the course of a couple hours, suggesting that the markers for the cells were being down-regulated, or blocked, rather than the cells being degraded. Also a further experiment in which lymphocytes were incubated in a 50/50 mix of normal medium and medium that was conditioned over F-98 cells showed the same loss of  $\text{CD 161}^+$  population. From this result it was concluded that a secretion from the F-98 cells was responsible for the  $\text{CD 161}^+$  population loss. Attempts were made to determine the nature of this secretion and its affect, but this remains an area where further study is necessary. These results also prevented a conclusion from being reached on the nature of the cells producing IFN-  $\gamma$ .

No Reported Students.

**CLINICAL RESEARCH FEASIBILITY FUND (CReFF)**

Specialty

Mentor Name

Funds Received

Period

Project Title

Attachment(s)

Project Summary

No CReFF Participants Reported.



## SCIENTIFIC HIGHLIGHTS

### Addictions Research

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SPID(s): 0051, 0468, 0470, 0536, 0560, 0598

PAST SPID(s):0220,0295,0605

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 investigators at the University of Connecticut Health Center (UCHC). 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 UCHC Alcohol Research Center (ARC), which is funded by the National Institute on Alcohol Abuse and Alcoholism (NIAAA), and Dr. Jonathan Covault, Associate Professor of Psychiatry, Director of the GCRC Core Laboratory and Director of the Molecular Genetics Laboratory of the ARC, have continued to examine candidate genes in the GABA system in relation to alcohol dependence. Together with Dr. Lance Bauer, they found that allelic variation in GABRA2, which maps to chromosome 4p, encodes the alpha-2 subunit of the GABA-A receptor, and has been shown in multiple studies to be associated to alcohol dependence, predicts the drinking behavior over time of individuals being treated with psychotherapy for alcohol dependence. In that study, they also found preliminary evidence of an allele X treatment interaction, representing a potential opportunity for individualized psychosocial treatment of alcohol dependence. Together with Drs. Howard Tennen and Tamlin Conner, Drs. Covault and Kranzler examined the effects of GXE on drinking and drug use in a sample of college students. They found that the short promoter allele of the serotonin transporter gene (SLC6A4) was associated with more frequent drinking and drug use among individuals who had experienced stressful events during the year preceding study enrollment. Together with Dr. Carlos Hernandez-Avila, Drs. Kranzler and Covault examined the pharmacogenetics of naloxone stimulation of plasma cortisol, which despite its inclusion of a putatively functional polymorphism in OPRM1, the gene encoding the mu-opioid receptor, differed as a function of European vs. Asian ancestry, suggesting the presence of a balancing polymorphism in Asians. Drs. Kranzler and Covault have also collaborated actively with Dr. Joel Gelernter of Yale University on studies of the genetics of alcohol and drug dependence.

Dr. Victor Hesselbrock, Chair of the GCRC Advisory Committee (GAC) and Principal Investigator of the NIH-funded ARC at UCHC, is a major collaborator in the multi-center Collaborative Study on the Genetics of Alcoholism (COGA). Dr. Hesselbrock provides a vital connection between COGA, which continues to lead the field of alcohol research in relation to the elucidation of the alcohol dependence phenotype and the genetic basis of the disorder, and the UConn ARC and GCRC.

Dr. Cheryl Oncken, Associate Professor of Medicine and Associate Program Director of the GCRC, completed a study of nicotine replacement in pregnant women, including a genetic substudy that was a major component of the last GCRC competitive renewal. Together with Drs. Naveed Hussain and Winfried Krueger, she completed a study of the effects of smoking on RNA expression in the umbilical cords of children born to mothers participating in the clinical trial.

Dr. Nancy Petry, Professor of Psychiatry, directs a highly productive program studying alcohol and drug dependence and compulsive gambling. The GCRC supported a number of studies of Dr. Petry, all of which continue to recruit actively. All studies are conducted at community-based treatment programs throughout New England. Dr. Lance Bauer has continued analysis of an NIH-funded project in the examination of cognitive control among patients with HIV/AIDS. In addition, he has developed an active program of research in relation to electrophysiologic and genetic predictors of the longitudinal course of alcohol and drug use among individuals with dependence on these substances.

### Publications:

Chen ACH, Tang Y, Rangaswamy M, Wang J, Almasly L, Foroud T, Edenberg HJ, Hesselbrock V, Nurnberger Jr. JI, Kuperman S, O'Conner SJ, Schuckit MA, Bauer LO, Tischfield J, Rice JP, Bierut LJ, Goate A, Projesz B Association of Single Nucleotide Polymorphisms in a Glutamate Receptor Gene (GRM8) with Theta Power of Event-Related Oscillations and Alcohol Dependence *Neuropsychiatric Genetics*

Grucza RA, Wang JC, Stitzel JA, Hinrichs AL, Saccone SF, Saccone NL, Bucholz KK, Cloninger CR, Neuman RJ, Bুদ্ধle JP, Fox L, Bertelsen S, Kramer J, Hesselbrock V, Tischfield J, Nurnberger Jr JI, Almasly L, Poresz B, Kuperman K, Schuckit MA, Edenberg HJ, Rice JP, Goate AM, Bierut LJ A Risk Allele for Nicotine Dependence in CHRNA5 is a Protective Allele for Cocaine Dependence *Biological Psychiatry*

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#### **Bone, Endocrine and Aging**

SPID(s): 0410, 0413, 0448, 0461, 0523, 0542, 0557, 0588, 0624, 0644 PAST SPID(s):0433,0597

KEYWORDS: BONE, ENDOCRINE, AGING

Drs. Pamela Taxel, Joseph Lorenzo, Carol Pilbeam 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 2008. She has two ongoing trials that include: a) omega-3 fatty acid supplementation in older, frail postmenopausal women that assesses bone, physical performance, and immune function and b) an 18-month intervention trial of protein supplement to assess bone and muscle effects (collaboration with Drs Karl Insogna (Yale) and Jane Kerstetter (University of Connecticut-Storrs)). 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. Dr. Faryal Mirza has completed a pilot study on the effect of estrogen deprivation with aromatase inhibitors on blood pressure in post-menopausal women which shows that 24 ambulatory blood pressure increases with estrogen deficiency, largely due to a rise in nocturnal systolic pressure. This study was presented at the annual Meeting of the Endocrine Society in June 2008.

#### **Publications:**

Taxel P, Kaneko H, Lee SK, Aguila HL, Raisz LG, Lorenzo JA Estradiol rapidly inhibits osteoclastogenesis and RANKL expression in bone marrow cultures in postmenopausal women: a pilot study. *Osteoporos Int* 19 193-9 2008

#### **DENTAL**

SPID(s): 0364, 0453, 0487, 0497, 0591, 0592, 0611, 0628, 0638 PAST SPID(s):0554

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, continues to collaborate with Drs. Oncken and Kranzler in a study of topiramate for smoking cessation, which uses daily interactive voice response (IVR) technology (supported by the GCRC) 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 cannabis abuse, and on short-term interventions for temporomandibular disorder (TMD). Interventions with TMD patients involve focused instruction in changing self-efficacy and decreasing "catastrophizing" with measurement outcomes including

real time" assessments of pain ratings, mood and coping (using computerized IVR) and changes in pro- and anti-inflammatory cytokines.

Dr. Robert Aseltine, Associate Professor of Oral Health and Diagnostic Sciences, has been active in screening, brief intervention, and referral efforts to reduce drinking among patients admitted to emergency departments in urban settings. He has been supported by the GCRC particularly through the use of interactive voice response (IVR) technology to obtain data longitudinally from individuals participating in these studies.

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. Anna Dongari-Bagtzoglou, Associate Professor of Oral Health and Diagnostic Sciences is investigating potential systemic effects of oral inflammatory processes, including oral candidiasis in kidney and heart transplant recipients and how periodontal infections and depressive symptoms affect the systemic inflammatory status of hemodialysis and pre-dialysis chronic kidney disease patients. Recent findings indicate that periodontal attachment loss emerged as a significant predictor of glomerular filtration rate (renal function deterioration in allograft transplant patients) after adjusting for cofounders. In addition, kidney and heart transplant recipients are infected with *Candida* in higher percentages, have higher titers and higher frequency of asymptomatic colonization than healthy controls.

Dr. Martin Freilich, Professor of Reconstructive Sciences, has begun a major observational study of bone health, especially osteoporosis, as a risk factor in bone augmentation and dental implant placement. This R01-funded project is expected to generate numerous hypotheses for further investigation.

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.

#### **Publications:**

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#### **Immunology**

SPID(s): 0496

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. Recent findings on the histopathologic response to tick bite in mice and humans have been submitted for publication. They suggest that human cutaneous hypersensitivity to tick bite may alter 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, Wikel, and colleagues are actively investigating the epidemiology and immunology of babesiosis in a highly endemic area. These studies include genetic determinants of resistance to human babesiosis in relation to aging.

**Publications:**

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## ADMINISTRATIVE NARRATIVES

### ADMINISTRATION

The General Clinical Research Center (GCRC) significantly restructured contract arrangements with Connecticut Children's Medical Center (CCMC). This was done to support pediatrics investigators better while making the most cost-effective use of funds. It entailed meetings over several months with research finance and administration managers at both entities, and pediatric investigators and study coordinators. Contract arrangements now include an umbrella memorandum of understanding between the GCRC and CCMC, and individual contracts for specific GCRC Advisory Committee (GAC) approved, GCRC-sponsored projects. Where clinical laboratory services are approved by GAC, additional associated contracts are established with Clinical Lab Partners (CLP), a wholly owned subsidiary of Hartford Hospital. As CCMC is on the same physical campus as Hartford Hospital, this allows investigators to use local resources, rather than working through the logistics of transporting samples for testing at UCHC with possible compromise of the samples.

The success of our prior year's data entry services "proof of concept" pilot encouraged fuller roll-out. This support service was expanded from double-data entry to include study-specific consultations on data management strategies, case report form design and SPSS database development, and data quality procedures and documentation. Staffing continues to be from the Informatics Core supervising student assistants. Funding for this activity continues to come from the School of Medicine.

This is the third year of administering a grant-making program funded by the Donaghue Foundation. The \$110,000 annual program is focused on bio-nutrition research of a practical benefit to Connecticut residents. It is open to investigators at the University of Connecticut (UConn) Storrs and Farmington campuses as well as local area hospitals and community-based organizations, who hold UConn academic appointments. Based on the Request for Proposal and scientific review processes, 5 projects were approved and funded. Three projects were approved the Institutional Review Board (IRB) and initiated during this reporting period.

Several deferred internal administrative projects were undertaken to organize and archive GCRC administrative and financial records. This included reviewing records retention requirements, working with investigators on inventorying, returning and purging research records and files, and relabeling research records to be consistent with study informed consent forms. We also began converting paper transaction detail to electronic images, and consolidating and documenting off-site storage holdings.

In preparation for the eventual transition from a GCRC to a clinical and translational science institute (CTSI), work began on developing fee-for-service operational centers for Core Laboratory, Informatics, Biostatistics, and Clinical (medical and dental) research services ("service centers"). The Service Centers were established as financial entities with published fee schedules. Services have been advertised to investigators on a limited basis and will be more broadly communicated in the future. Manual cost-tracking and billing functions have been developed but are being refined as UConn plans for CTSI governance and technical infrastructure.

## **BIostatistician**

The Biostatistics Core worked with established and potential GCRC investigators in the development and design of new research projects. It also performed analysis of data from GCRC protocols and guided GCRC investigators and staff members in conducting their own data analyses. Core staff included the director (Dr. Stephen Walsh, 30% annual effort) and a master's-level statistician (Ms. Deborah Dauser-Forrest, 25% annual effort). 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. He also presented a lecture on sample size and power in the Clinical Research Coordinator's Course sponsored by the Clinical Core and a session on study design in the program for summer research scholars. Ms. Dauser-Forrest conducted data analysis for GCRC projects under the direction of Dr. Walsh and monitored subject recruitment to GCRC protocols to document each protocol's progress in achieving recruitment objectives.

## **Core Lab**

During the April 2007 - March 2008 year 14 grant period, the Core Laboratory reported 41,050 assay results, an increase of 34% compared with year 13. These included 2,924 hormone or protein analyte results, 33,397 genotype results, 248 DNA sequence analysis of PCR amplicons, isolation of DNA or RNA from 3,444 samples, and analysis of 228 blood samples by FACS.

During this past year we used institutional funds to replace a -80°C freezer and purchase a 384-well PCR thermocycler to support higher volumes of genotyping assays. Migration of our sample data base to the FreezerWorks software system purchased in year 13 has been completed. All archived as well as new samples are now included in our FreezerWorks sample storage and tracking database. This has significantly improved our ability to manage thousands of archived samples for more efficient staff time use.

The largest growth area for assay requests is in the area of genetics and gene expression. When possible, to avoid duplication of equipment, we continue to make use of resources in other UCHC labs to support this need. The Core Lab has developed partnerships in the past year with the Translational Genomics Core at UCHC to provide microarray services for GCRC protocols including gene expression and DNA methylation arrays. One such project used gene expression array coupled with qPCR in the Core Lab to identify smoking-related changes in umbilical cord gene expression. These results were recently accepted for publication in *Pediatric Research*. Due to the increased requests for examination of epigenetic DNA methylation levels by investigators, Core Lab staff have recently been trained in use of a shared instrument (Biotage Pyrosequencing Work Station) for quantitative CpG methylation assays to respond to investigator needs. The instrumentation would also allow the Core Lab to provide quantitative single nucleotide polymorphism (SNP) allele frequency from pooled case-control studies. Finally, we have partnered with two other laboratories to maintain and use a robotic liquid handling work station to more efficiently prepare 384-well sample plates for genotyping.

The Core Laboratory continues to be licensed by the State of Connecticut Department of Public Health with a CLIA certification. In 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 (IVR). The IVR system, which was acquired in the Fall of 2002, continues to grow. The system, used to host and administer phone-based interviews, has been expanded to include 90 telephone lines that are made available to administer questionnaires. Since inception, the system has supported 21 studies with 15 studies being active in Year 14. In addition to supporting investigators at UConn, IVRS has hosted studies for investigators from other institutions, including Yale University, the University of Michigan, the University of Chicago, and Arizona State University. In the past year, the system administered over 15,000 calls to 576 study participants, lasting approximately 1,000 hours. This effort has thereby substantially reduced study 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, Informatics Core Director, and his staff.

Data Entry. The GCRC has expanded the data entry service it offers investigators. We have a well-trained team of three undergraduate students who enter data for studies approved to use this service, using the SPSS Data Builder/Workstation modules. Once the data have been double entered and verified, they are made available for checking and analysis, and subsequent export to other applications and formats. Currently the data entry team has 11 approved studies being developed or in active entry. Several more studies are pending IRB approval to be initiated.

Fileshare. The GCRC has provided investigators disk space on a high capacity, high availability file server to store study data and other protocol related files. Access to the fileshare is based on a role-based access permission schema that allows investigators and their staff to access their protocol folder and data only. In addition, the file server contains group and personal folders for GCRC staff.

Research Portal. The Informatics Core is leading efforts at UConn to develop a web-based research portal. The first phase of the portal is the creation of a recruitment registry, where interested members of the public visit the portal, learn about clinical research, search for clinical studies, and self-enter their information in the registry. Investigators will be able to search the registry for potential volunteers. We anticipate this registry would serve as an invaluable tool in recruitment efforts in clinical research at UConn. The initial design and development work was completed, with roll-out of the new recruitment registry expected in July 2008. The second phase of the portal is the development of a registry of investigators and their area of research interest/expertise. We hope this investigatory registry will serve as a matchmaking vehicle to help promote interdisciplinary research.

Administrative Software. The Informatics Core provides technical support to several internal applications. 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 third year of production. A number of reports and features continue to be added to the system to enhance data quality and increase the system's utility in the ongoing operation of the GCRC as well as supporting NIH reporting. Additionally, several commercial software packages are used: Freezerworks (to track specimens in storage freezers), Grant Manager (to manage GCRC finances), and Personnel Manager (to project and track payroll expenses and time and effort).



## NURSING

The Clinical Core continues to use a combination of clinical research nurses and clinical research assistants (CRAs) to meet current and anticipated research study needs. Currently, the Clinical Core consists of 5 nurses who are research facilitators (RFs) (4 full-time, 1 part-time), 1 clinical research nurse (CRN), 3 clinical research assistants (CRAs), and 2 dental assistants (DA, 1 part time and 1 full time), each of whom coordinates 4-9 clinical research protocols. Of 8 staff eligible for certification by the Society of Clinical Research Associates (SoCRA), 7 are currently certified.

Personnel Changes - In the last year, changes in the Clinical Core included the departure of an APRN, Michelle Kelly and the hiring of a CRA, Paul Appleton. Paul was hired to replace veteran CRA, Laura Glynn, who graduated from nursing school in May 2007 and took a position in an acute care facility. Paul Appleton, MD, comes to the GCRC with little research experience, but with greater than 10 years experience in anatomical and clinical pathology. He is funded by the GCRC grant at 50% time, coordinating 2 trials, and he receives 50% salary support on an NIDDK grant to one of the GCRC investigators. Dr. Appleton is in the process of applying for medical credentialing through the University's Medical Staffing Office. This will enable him to assist investigators by conducting physical examinations and minor medical procedures.

Thomas Kiely, RNC, Nurse Manager, continues to review currently active GCRC clinical studies to identify the clinical staff expertise and time and effort needed. Over the last year the clinical research teams, generally consisting of an 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) usually 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 clinical skills necessary to complete all phases of the clinical contact.

For the sixth year, the Clinical Core sponsored a two-day Clinical Research Coordinators Course. The course provides participants with 12 Connecticut Nurses' Association continuing education units (CEUs), which are approved by the American Nurses Credentialing Center's Commission on Accreditation. The course serves to introduce to CRAs, technicians, nurses, and others interested in study coordination the principles of clinical research. It consists of didactic presentations and the identification of relevant resources by experienced research personnel. The course goal is to promote a conceptual awareness of what distinguishes clinical research from clinical practice. There are 12 hours of sessions led by staff from the GCRC, Clinical Trials Unit, Human Subjects Protection Office, and the Investigational Pharmacy Service. The course covers the research process, with an emphasis on the many facets of study coordination that are necessary for safe and effective clinical research. Specific 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**

## Other - Dental

NCCR approved both interim and final relocation plans for the Dental Clinical Research Center (DCRC). Architect drawings are nearly complete for the renovation of a new facility being accomplished with \$300,000 in UConn support and \$50,000 of industry in-kind gifts. This clinic will be a state-of-the-art, attractive facility containing three operatories, a patient waiting room, a business office, dirty and clean preparation rooms and a small dental laboratory. Dental faculty were engaged in 8 active studies (approximately \$3,000,000 in direct costs during this fiscal year) most of which will continue into fiscal year '08- '09. In the past year the DCRC accommodated one new R01 and a GCRC-funded pilot project. Staffing remained stable during the year with our 1.6 FTE dental assistants functioning well together in study coordination and research patient contact functions.

## Other - Education and Training

This was an important year for our activities in education and training. Under the leadership of Dr. Anne Kenny, a Master of Science in Clinical and Translational Research (MSCTR) was developed, approved by the University and the Connecticut Board of Higher Education and accredited. The first class began in September 2007 with 5 students and was the major formal didactic offering in clinical research. The program graduated its first student in May 2008.

The GCRC course "Principles of Clinical Research" was quite successful during the past few years under the leadership of Dr. Howard Tennen. The course was suspended during the past year, to make it possible to initiate the MSCTR. The course is being transitioned to an on-line offering with plans for 22 video lectures, related readings and monthly face-to-face meetings with course leaders. The transition to the on-line course is nearly complete and the new course will be offered beginning in the fall 2008. Plans are for the course to be offered three times annually in the fall, spring, and summer sessions.

This was another stellar year for GCRC-sponsored seminars. From September 2007 through June 2008, a total of 19 seminars were held, with an average attendance of 35 people at each seminar.

We had eight summer fellows sponsored by the GCRC in the summer of 2007, two college students, five medical school students and a dental school student. The summer student seminars on clinical research, which ran for eight weeks, were open to all summer students at the Health Center and were attended by 11 students each week.

**PROGRAM DIRECTION**

Bruce Koeppen, MD, PhD, Dean of Academic Affairs and Principal Investigator. for the 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.

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.

The leadership of the GCRC continues to include three Associate Program Directors. Anne Kenny, M.D., Associate Professor of Medicine, Cheryl Oncken, M.D, M.PH., 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 M01 support for these individuals, so that the total support for the Associate Program Directors from the GCRC grant is 0.30 FTE. Lesley Mancini, M.B.A. continues as the Administrative Director and Thomas Kiely, R.N.C. is the Nurse Manager and Director of the Clinical Services Core. The directors of the other cores remain unchanged. Jonathan Covault, M.D, PhD. 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., Ph.D. continues as Director of the Dental Clinical Research Core; and Stephen Walsh, Sc.D. continues as Director of the Biostatistics Core. Kathleen Salomone, A.P.R.N., M.S.W., continues in the role of Research Subject Advocate (RSA), a 70% position. Ms. Salomone's position also includes 30% time with the UCHC Human Subjects Protection Office (which oversees the functions of the UCHC Institutional Review Boards), supported by institutional funds. Ms. Rene Bumbera has replaced Ms. Theresa George in assisting Ms. Salomone in discharging the duties of the RSA.

**RES SUBJECT ADVOCACY**

Kathleen Salomone, MSW, APRN continued in her role as Research Subject Advocate (RSA) for the GCRC, reporting to Dr. Bruce Koeppen and working closely with Dr. Henry Kranzler (GCRC Program Director), Dr. Victor Hesselbrock (Chair of the GAC), GCRC staff and investigators and the Human Subjects Protection Office (HSPO) of UConn Health Center.

Ms. Salomone reviewed all protocols submitted to SAC requesting GCRC resources at the time of initial application and annual continuation . She ensured that every protocol reviewed by GAC had a Data and Safety Monitoring Plan/ Board commensurate with the study risk. At the time of annual continuation she also reviewed protocol deviations and adverse events and communicated any concerns to GAC.

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 kept pertinent GCRC staff informed regarding lapses in IRB approval for GCRC supported protocols.

Ms. Salomone conducted random audits of protocols supported by GCRC resources. The audits are a quality management tool providing a systematic internal process to oversee subject safety, ensure that monitoring is being conducted in accordance with the IRB-approved DSMP/B and increase compliance with federal, state and institutional requirements. Within the GCRC, she participated in the GAC, Executive Committee and Project Review and Initiation Team (PRIT). Additionally, she attended quarterly meetings of the UConn Office of Audit, Compliance and Ethics and acts as a GCRC liaison with that office.

Ms. Salomone worked closely with the Human Subjects Protection Office (HSPO) in providing appropriate monitoring of GCRC supported studies, overseeing implementation of HSPO policy changes within the GCRC and for all GCRC supported protocols. She represented GCRC concerns to the UCHC IRB chairs and to the IRB chairs at collaborating institutions. Ms. Salomone served on the HSPO Executive Council, which acts as an advisory board to the Director of the Human Subjects Protection Office on matters of policy, regulations and issues related to human subject protections.

Ms. Salomone also worked with research staff at the Connecticut Children's Medical Center (CCMC), a UCHC collaborating institution, and the UConn Storrs campus. She assisted investigators with properly invoking the IRB Cooperative Agreements between UCHC and their respective institutions.

Finally, Ms. Salomone served on the Research Adverse Events Committee, a sub-committee of the HSPO. This committee is charged with reviewing research-related serious adverse events (SAEs) with the mission of protection of research subjects. She served as one of three primary reviewers of SAEs submitted via the mandatory UCHC on-line reporting system.

**RESEARCH BIONUTRITION**

Not applicable.

**COMMITTEE MEMBER INFORMATION**

\*Chairperson

**Committee Member**  
**Area of Expertise**  
**Department**  
**Institution: State, Country**

**Committee Member**  
**Area of Expertise**  
**Department**  
**Institution: State, Country**

**ADVISORY COMMITTEE (Internal)**

\*HESSELBROCK, VICTOR PHD

Psychiatry  
 Psychiatry

BAUER, LANCE PHD

Psychiatry  
 Psychiatry

BURKI, NAUSHERWAN K MD

Medicine  
 Medicine/Pulmonary Medicin

FIFIELD, JUDITH PHD

Family Medicine  
 Family Medicine

GRAVELEY, BRENTON PHD

Genetics and Developmental Biology  
 Genetics and Developmental

KELLY, JOHN R (Non-Voting) DDS, DSC

Dental  
 Oral Rehab, Biomaterials

KIELY, THOMAS (Non-Voting) BSN

Clinical Core Director, GCRC  
 GCRC

KRANZLER, HENRY (Non-Voting) MD

Psychiatry  
 Psychiatry

MANCINI, LESLEY (Non-Voting) MBA

Administrative Director, GCRC  
 GCRC

PILBEAM, CAROL MD, PHD

Medicine, Geriatrics  
 Medicine

SALOMONE, KATHLEEN (Non-Voting) RN

Research Subject Advocate  
 GCRC

WAGNER, JULIE PHD

Behavioral Health/Psychiatry  
 Behavioral Sci & Comm Hlth

WOLFSON, LESLIE MD

Neurology  
 Medicine/Neurology

\*RAJAN, THIRUCHANDURAI V MD, PHD

Immunology  
 Pathology

BURKE, GEORGINE (Non-Voting) PHD

Research Administration, CCMC  
 PEDIATRICS  
 CONNECTICUT CHILDREN'S MEDICAL CT USA

COVAULT, JONATHAN (Non-Voting) MD, PHD

Psychiatry  
 Psychiatry

FURNEAUX, HENRY PHD

Vascular Biology  
 Center for Vascular Biolog

HAGADORN, JAMES MD

Neonatology, CCMC  
 NEONATOLOGY  
 CONNECTICUT CHILDREN'S MEDICAL CENTER CT USA

KENNY, ANNE (Non-Voting) MD

Medicine, Geriatrics  
 Center on Aging

KOEPPEN, BRUCE (Non-Voting) MD, PHD

Medicine  
 Medicine

LALLA, RAJESH BDS, PHD

Oral Health and Diagnostic Sciences  
 Oral Diagnosis

ONCKEN, CHERYL (Non-Voting) MD

Medicine  
 Medicine

RAISZ, LAWRENCE G (Non-Voting) MD

Medicine  
 Medicine/Endocrinology

TANNENBAUM, SUSAN MD

Hematology-Oncology  
 Medicine/Hem-Onc

WALSH, STEPHEN J SCD

Biostatistics  
 Ctr for Biostatistics

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