Case Western Reserve University
Principal Investigator: Nathan Berger, MD

The overall goals of the Case Center for Transdisciplinary Research on Energetics and Cancer are defined organizationally and scientifically. Organizationally, we seek 1) to establish a productive, durable program for transdisciplinary research on energetics and cancer at Case Comprehensive Cancer University, 2) to provide pilot project support and training opportunities for new and established scientists who can conduct integrative research on energetics, energy balance and their consequences relative to cancer across the continuum from cancer causation and prevention through survival, and 3) to establish collaborative relations with investigators throughout our university and at other TREC Centers and universities to maximally and synergistically utilize resources to significantly impact problems associated with obesity and cancer. Scientifically, we will conduct a spectrum of mechanism-based laboratory, clinical, and population-based studies to identify targets for prevention and control of obesity and interruption of the linkage between obesity and cancer. The scientific aims are defined by three programs and two initial pilot projects, which are highly interactive and are supported by three TREC core facilities and by the 17 Comprehensive Cancer Center core facilities.

Project 1: Obesity and Molecular Pathways Leading to Colon Cancer
Principal Investigator: Sanford Markowitz, MD, PhD

Colon cancer is the second leading cause of cancer death in the U.S., and in the obese population the risk of developing colon cancer is elevated by 2-fold, which is among the largest increases in risk seen for any obesity associated cancer. The goals of this project are to demonstrate that increased colon cancer risk is associated with obesity per se, and not with increased dietary fat intake, to elucidate the role of increased IGF1 signaling as a mediator of the obesity associated increased colon cancer risk, and to further identify key genes whose expression within the human colon is altered by obesity and by altered IGF1 signaling. This project is based on the unique development by our group of C57bl/6 derived chromosome substituted mouse strains that are either obesity sensitive or obesity resistant when placed on a high fat diet, and also on the unique finding by our group of mutational activation of IGF1 signaling in frank colon cancers due to mutational activation of PIK3CA, an early transducer of IGF1 signaling. Our specific studies will be:

i) To compare the intestinal tumor promoting effects of high fat diet in mice that become obese on this diet (obesity sensitive) versus mice that do not develop obesity (obesity resistant), when these mice are engineered to carry the intestinal tumor inducing APC mutant Min allele.

ii) To employ expression microarrays to identify those mouse genes whose expression in the intestine is regulated by obesity, that is genes whose expression is modulated by a high fat diet only in obesity sensitive, but not in obesity resistant mice. To further identify which of these obesity regulated genes demonstrates altered expression in a microarray comparison of colonic epithelium from obese versus non-obese humans.

iii) To construct transgenic mice in which an activated mutant PIK3CA gene is specifically targeted for expression in the intestine. Further, by comparing tumor development in obese versus non-obese mice carrying this transgene, to determine whether the tumor promoting effect of activated IGF1/PIK3CA pathway signaling is epistatic with (in the same pathway with), or is independent of the tumor promoting effects of obesity.

iv) To compare the activation of IGF1 signaling in normal human colon mucosa from obese versus non-obese individuals by using quantitative immunohisochemistry to compare in these tissues the levels of phosphorylation of key IGF1 activated signaling molecules: IGF1R, AKT and mTOR. Moreover, to identify those genes whose expression in the mouse intestine is altered by increased IGF1/PI3KCA signaling, and to further identify if this "IGF1 signaling signature" of altered gene expression is evidenced on microarray comparison of gene expression in the colons of obese versus non-obese humans.

Project 2: Insulin Resistance Syndrome Pathway Factors and Colon Polyps
Principal Investigator: Li Li, MD, PhD

Increasing evidence from both model systems and epidemiologic studies support that insulin resistance resulting from long-term energy imbalance plays an important role in colon carcinogenesis. The fact that the incidences of obesity, insulin resistance syndrome, and type 2 diabetes are escalating at epidemic pace worldwide makes the exploration of the insulin resistance-colon neoplasia hypothesis a subject of pressing priority. We hypothesize that candidate genes and associated biomarkers in the insulin-growth hormone-insulin-like growth factor (IGF)-insulin receptor substrate 1 (IRS-1) axis, adipogenesis pathway (adiponectin, and peroxisome proliferator-activated receptor-y), and dietary factors may work jointly to drive the development of insulin resistance syndrome, and subsequently, the development of colon adenomatous polyps, established precursors of colon cancer.

We propose a screening colonoscopy-based incident case-control study to address the insulin resistance syndrome-colon polyp hypothesis by prospectively recruiting 750 incident colon polyp cases and 750 frequency-matched controls.

We will determine the candidate gene variants and haplotypes, associated biomarkers, and insulin resistance syndrome related serum markers using blood samples, and collect dietary and lifestyle risk factor information using questionnaires. We will analyze the resulting information using novel statistical models to gain comprehensive understanding of the link between insulin resistance syndrome and colon polyps. Specifically, we will 1) to investigate the impact of insulin resistance syndrome as an integral entity on colon polyps; 2) to examine the impact of candidate genes and associated biomarkers in the insulin-GH-IGF-IRS axis and adipogenesis pathway on colon polyps; 3) to evaluate the association of dietary patterns, glycemic index and glycemic load with colon polyps; and 4) to synthesize the information on candidate genes, biomarkers, and diet by looking at their joint effects on colon polyps, and to comprehensively evaluate these factors' potential direct as well as indirect (mediated by insulin resistance syndrome) impact on colon polyps.

Our study will contribute to our understanding of how insulin resistance syndrome pathway-related candidate genes and dietary factors might work in concert in the etiology of colon adenomatous polyps. Our study may have profound implication for public health prevention/intervention strategies targeting at the early stages of the colon adenoma-cancer continuum.

Project 3: Determinants of Obesity and Metabolic Dysfunction in Adolescents
Principal Investigator: Susan Redline, MD, MPH

Obesity and metabolic dysfunction increase the risk of cancer incidence and mortality. Increases in obesity and associated metabolic dysfunction are likely partly attributable to

modern lifestyles characterized by high fat food intake and reduced physical activity, and such behaviors may begin in childhood. Insufficient sleep, increasingly common in adolescents, has been implicated as a risk factor for both obesity and metabolic dysfunction. In this project, we will define the relationship between a number of host risk factors operating during childhood and adolescence, including insufficient sleep and sleep apnea, to longitudinally measured changes in both weight and biochemical indices of metabolic pathways implicated in cancer. We will capitalize on access to a large population-based pediatric cohort, the Cleveland Children's Sleep and Health Study, in which multiple measures of behavioral, sleep and biochemical risk factors for obesity have been measured longitudinally. The sample includes 50% former preterm children and 41% ethnic minorities, providing opportunities to quantify and identify specific mediators of excess risk of obesity and metabolic dysfunction in vulnerable subgroups. We propose to study 600 cohort members at ages 16 to 19 years, obtaining current measures of metabolic function that have been implicated in cancer (i.e., sex hormone levels, insulin resistance, adipokines, growth factors). Anthropmetric measurements will quantify body weight, stature, and body fat distribution. Risk factor data include standardized assessments of nutritional intake and behavioral risk factors. Subjects also will undergo 5-7 day monitoring of physical activity level and sleep/wake behavior with actigraphy and an overnight sleep study. Combining these data with birth data and data collected at a previous 8 to 11 year old exam will allow us to address the hypothesis that weight gain is largest in adolescents with insufficient sleep, and such effects are independent of other behavioral risk factors; and that metabolic dysfunction is most marked in adolescents with sleep apnea and in those with rapid weight gain. Identification of risk factors for obesity and metabolic dysfunction, and their variation with demography and common behavioral factors, including the novel consideration of sleep behaviors, may help develop targeted interventions for high-risk children and elucidate important pathophysiological pathways that increase risk of several chronic health conditions, including cancer and diabetes.

Fred Hutchinson Cancer Research Center
Principal Investigator: Anne McTiernan, MD, PhD

The TREC Research Center at Fred Hutchinson Cancer Research concentrated on prevention of breast and colorectal cancers, with particular emphasis on diet and physical activity. The projects included an integrated research program that examined energy balance and its consequences in cells, animal models, and human subjects. We propose in the Seattle TREC Center to elucidate the pathways linking components of energy balance to the cancer process using several different study designs, with the transdisciplinary contributions of scientists from medicine, cell biology, animal models, epidemiology, nutrition, gastroenterology, molecular biology, obesity, endocrinology, obesity, cardiology, immunology, biostatistics, mathematics, exercise physiology, and behavioral science. The overarching theme of the Seattle TREC Center will be determining the mechanisms by which energy balance modifies and influences the process of carcinogenesis across the lifespan in a broad range of settings including cell culture, animal models, small-scale human experimental studies, and population-level experimental work. In Project 1 we will bring together basic research efforts underway in our laboratories in an innovative approach to analyzing the cellular effects of hyperglycemia, hyperinsulinemia, and inflammation on growth, proliferation and survival pathways relevant to oncogenesis. In Project 2 we will determine, in an animal model, the effects of caloric restriction and exercise, alone and in combination, on the carcinogenic response in the mammary gland and on the mechanisms by which changes in energy balance modulate the development of cancer. In Project 3 we will investigate the metabolic and cancer biomarker response to experimental high and low glycemic load diets in lean and obese teenagers and young adults in a crossover clinical trial design. Within a randomized controlled trial in Project 4, we will investigate the effects of dietary weight loss and exercise, alone and together, on biomarkers of inflammation, and DMA damage and repair, and the influences of genetic polymorphisms on these associations. In Project 5 we will test a worksite obesity prevention intervention in a geographic area with large representation or low income and minority individuals on body mass index and markers of insulin resistance and inflammation. Our novel laboratory work will include testing intervention effects on serum proteomics and, in a developmental project, on metabolomics, in order to identify biological signals of dietary, exercise, and adiposity. Our investigators have a wealth of expertise in the components of the energy balance and cancer equation, and will provide important scientific leadership, training, and contributions to the overall TREC program.

Project 1: Linking Nutrient Supply & Cell Cycle Survival
Principal Investigator: David Hockenbery, MD

Nutrient availability affects cell growth, proliferation and survival. Apart from pancreatic beta cells, skeletal myocytes, adipocytes and hepatocytes, there is a dearth of information about how cells respond to positive energy balance in the whole animal. Using endothelial cells as a prototypic cell lineage that is resistant to transformation, we will characterize cellular responses to the availability of a nutrient source, glucose, in excess of metabolic requirements (relevant to Projects 2, 3). High concentrations of external glucose trigger an autoregulatory mechanism to limit both glucose uptake and growth factor signaling, while stimulating intracellular pathways that regulate cell proliferation and apoptosis (examined in Project 2). Specifically, we have found that incubation of primary endothelial cells in 25 mM glucose induces c-myc transcription, activation of NF-icB pro-inflammatory pathways and downregulation of PI3-K/Akt signaling (relevant to Projects 2,4) in this cell type. These findings extend a growing appreciation that oncogenes, tumor suppressor genes, and signal transduction pathways are tightly coupled to changes in nutrient availability and energy metabolism. Having established how proliferative

responses are coupled to nutrient excess in cells that resist transformation, we will investigate how primary mammary epithelial cells respond to excess glucose availability/We hypothesize that cells that are susceptible to neoplastic transformation will exhibit distinct identifiable responses to nutrient excess that favor cell proliferation. Finally, we will determine whether immortalized, initiated mammary epithelial cells exhibit heightened sensitivity to the effects of glucose excess, providing an epigenetic mechanism for tumor promotion. This project addresses key questions for obesity and cancer risk: how nutrient excess is coupled to changes in cell proliferation and survival, and at which point in carcinogenic progression does energy balance become critical. Insights gained from these investigations will provide novel frameworks for analyzing the effects of obesity on site-specific cancers in animal models and human populations (relevant to Projects 2-5).

Project 2: Energy Balance and Cancer: Markers and Mechanisms in Rats
Principal Investigator: Henry Thompson, PhD

The goal of this project is to determine the effects of controlling weight gain by energy restriction, physical activity, or their combination on the carcinogenic process in an experimental model for breast cancer, and to assess how dietary carbohydrate availability modulates responses as outlined in the followings aims. Aim 1. Determine the effects of energy restriction or physical activity alone or in combination on the carcinogenic response in the mammary gland and on candidate markers for cancer risk. This model is built on the human model in Project 4 but extends observation to related pathways/processes in the target tissue. This work will be conducted using a well characterized rodent model for breast cancer and a rodent exercise device newly developed by our laboratory in which a variable speed, motorized activity wheel is linked, under computer control, to a food pellet dispenser so that physical activity behavior is maintained by positive food reward. Effects of these interventions on the carcinogenic process, on factors involved in glucose homeostasis, and on indicators of inflammation and oxidative damage will be measured. As in Project 1 we will seek to determine how cell proliferation, apoptosis, and angiogenesis are modulated. Aim 2. Assess the effect of carbohydrate availability on the carcinogenic response and systemic biomarkers when weight control is mediated by energy restriction and observe of pathways and processes in the target tissue. There is considerable speculation but few experimental data to inform the debate about the consequences on disease risk of popular weight loss/maintenance diets that differ in carbohydrate availability. Preliminary studies have established the feasibility of feeding the same diets used in the human feeding study proposed in Project 3 in our pre-clinical animal model. Aim 3. Investigate candidate mechanisms and markers using genomic and proteomic technologies in order to elucidate target pathways for prevention. Human beings vary in the amount (dose) of energy restriction or physical activity in which they engage to control weight. Available pre-clinical data indicate that different mechanisms may underlie the prevention of cancer by these interventions depending on intervention dose. cDNA microarray analyses will be used to detect differences in the pathways induced in response to energy restriction or physical activity dose and proteomic technologies performed in Core C will be employed to discover serum biomarker profiles that reflect the modulation of the carcinogenic response by these interventions.

Project 3: Glycemic Load and Obesity Effects on Cancer Biomarkers
Principal Investigators: Marian Neuhouser, PhD, RD and Johanna Lampe, PhD, RD

Nearly two-thirds of the adult population of the United States is overweight or obese. One of the serious consequences of this obesity epidemic is the growing evidence that obesity increases risk for several common cancers. Hyperinsulinemia, and altered levels of adipocyte hormones,

insulin-like growth factors and markers of inflammation often accompany obesity and may provide the mechanistic explanation for these observed associations of obesity with cancer. IGF-1 inhibits apoptosis and stimulates proliferation and both insulin leptin are mitogenic. On the other hand, obesity inhibits adiponectin, which has been associated with both the inflammatory response and carcinogenesis. Dietary patterns are related to the synthesis, metabolism and distribution of these biomarkers. For example, diets can be characterized relative to their influence on the postprandial glucose response; e.g., diets rich in simple sugars and refined carbohydrates have a high glycemic index because they produce a rapid rise in blood glucose. Foods such as meats, legumes, and high-fiber fruits and vegetables produce a low rise in blood glucose and have a low glycemic index. Despite the plethora of scientific papers suggesting that high-glycemic-index foods increase cancer risk, very few intervention studies in humans have evaluated the action of low and high glycemic foods on biomarkers of cancer risk. We propose a randomized, controlled cross-over feeding trial in 88 lean (BMI<25) and obese men and women (BMI>30). Participants will be randomized to consume either a low- or high-glycemic- load diet for four weeks, followed by a four-week wash-out period, then cross-over to the other arm. Blood samples will be collected at the beginning and end of each diet period and assayed for insulin, glucose, IGF-1, IGFBP3, leptin, adiponectin, C-reactive protein, serum amyloid A, and interleukin-6. This study will provide a rigorous test of common dietary patterns in humans that will allow us to directly test diet-related mechanisms of obesity and biomarkers of carcinogenesis. Importantly, by recruiting both lean and obese persons, we will be able to examine whether there is a differential response to the high- and low-glycemic load diets for lean vs. obese individuals. This study will provide data of immediate clinical and public-health benefit.

Project 4: Exercise and Diet: Biomarkers and Mechanisms in Humans
Principal Investigators: Neli Ulrich, PhD and Anne McTiernan, MD, PhD

Physical activity and nutrition alter cancer risk with possible mechanisms including effects on inflammation, insulin-like growth factors, insulin resistance, steroid hormones and lipid metabolism. A yet unexplored possible mechanism linking energy balance to cancer risk includes effects on DNA repair capacity. Defects in DNA repair function are clearly carcinogenic and intriguing preliminary evidence suggests that regular exercise results in an adaptive response of enhanced antioxidant defenses and DNA repair. DNA repair capacity also plays a central role in that inflammatory process can increase oxidative DNA damage.

The proposed Project 4 of the Seattle TREC will address the intersection of diet, physical activity, weight, and body composition on biomarkers of cancer risk. The research will be ancillary to a funded human clinical trial of exercise and caloric restriction. Primary specific aims are to investigate the separate and combined effects of 1-year of exercise and/or a reduced-calorie diet among 503 postmenopausal women on 1) biomarkers of inflammation (C-reactive protein, serum amyloid A, interleukin-6), 2) DNA damage sensitivity and DNA repair capacity, and 3) plasma protein patterns (proteomics) Investigations of intervention effects on plasma protein patterns will enable us to identify possible new mechanisms linking exercise or a reduced calorie diet to carcinogenesis. As secondary outcomes we will evaluate intervention effects on gene expression of DNA repair genes and on biomarkers of obesity. Further, we will investigate whether intervention effects differ by body mass index or body composition prior to the intervention or dependent on changes in body composition during the course of interventions. Finally, we will explore whether genetic characteristics modify the intervention effects. The proposed measurements will be complemented by biomarkers already planned within the funded parent grant (insulin, IGF1, IGFBP3, steroid hormones) and allow for investigations of interactions with the newly investigated pathways. Thus, Project 4 provides a

comprehensive and cost-effective approach for investigating the independent and combined effects of exercise and caloric restriction on biomarkers of cancer risk among humans. Close collaborations with Projects 2, 3, and 5 will enhance our understanding of the mechanistic effects linking exercise and energy balance to cancer risk.

Project 5: Preventing Obesity in Low Income Working Adults
Principal Investigator: Shirley Beresford, PhD, MS, MA

Reducing the prevalence of obesity in the population is one of the Healthy People 2010 goals, and active vigilance is required in all age groups in preventing and reversing overweight and obesity. On a population basis, the prevalence of overweight is associated with a myriad of influences, including social, behavioral, cultural and environmental factors as well as genetic and physiological factors. For a majority of overweight individuals, restoring a balance between energy intake and expenditure is difficult, and therefore there is an increasing emphasis on preventing obesity on a population level. The longer-term goal of this research is to prevent further increase in rates of obesity in the population. This project has the potential to influence the worksite environment in ways informed by this Center's other projects.

In the adult population of working age, a majority of the day is spent in the worksite, suggesting that interventions at the worksite level may offer the opportunity for success in this age group. We propose to develop and test a comprehensive intervention with simple messages that will integrate changes in dietary intake with changes in energy expenditure, while simultaneously modifying structural and environmental factors to promote social support and opportunities for behavioral change. We will recruit and randomize 28 worksites, from the 98144 zip code area, to a two year intervention in which we will: build a physical activity intervention combining increased daily physical activity and regular, structured exercise; build a dietary intervention that will promote lower calorie intake; increase worksite access to both healthy foods and physical activity. Our primary aim is to evaluate the effectiveness of the intervention in reducing or maintaining body mass index in a randomized controlled trial of worksites. We will compare changes in body mass index in intervention versus control worksites using two cross-sectional surveys at baseline and follow-up. The impact of the intervention on biomarkers related to nutritional intake, obesity, inflammation, insulin resistance and adipokines will be estimated in a subset of employees. Our team has considerable experience with interventions at the worksite level and substantial expertise in obesity prevention. We anticipate that this project will yield important contributions to the implementation of obesity prevention and will be informed by study results obtained in Projects 1-4.

University of Minnesota
Principal Investigator: Robert Jeffrey, PhD

The University of Minnesota TREC Research Center focused on population studies that examined the causes of, and effective prevention strategies for, obesity in youth and families. The purpose of this center proposal is to conduct transdisciplinary research, training, and outreach on obesity and cancer in youth, family, and young adults. The proposed Center will address questions about the etiology, prevention, and treatment of obesity in youth and families, and explore biological pathways that may link obesity to cancer. The center proposal includes three specific research projects. Project 1 is a multifactorial, cross-sectional, and prospective observational study examining predictors of obesity development in adolescents, including sociocultural factors, family factors, environmental factors, and individual factors. Project 2 is a study evaluating family-base, weight-gain prevention intervention that particularly emphasizes intervention on environmental contributors to weight gain. Project 3 is a study of the effects of physical activity on estrogen metabolism, oxidative stress, and DNA repair mechanisms in young women. The three R01 grants will be supported by two cores, an Administrative Core and a Data Services and Analysis Core. The proposal also includes a career development component, substantial funding for developmental projects, and a dissemination/translation component. The overall goals are to advance transdisciplinary science in the advancement of understanding of obesity, youth, family, and cancer; to support the career development of new investigators in the field; and to disseminate scientific knowledge about the topic to broader audiences.

Project 1: Etiology of Adolescent Obesity
Principal Investigator: Leslie Lytle, PhD

This research will examine cross-sectional and prospective predictors of adolescent obesity using a social-ecological framework. We will recruit 420 youth and one of their parents from an existing cohort of youth who are currently participating in the Minnesota Adolescent Community Cohort (MACC) study. The MACC cohort is a representative sample, drawn from 60 geopolitical units throughout the state of Minnesota, and has been followed for 4 years as part of a study examining the effects of state and local tobacco programs on youth tobacco use. Dr. Jean Forster is the Principal Investigator for this on-going study. For our TREC research, we will invite students in the MACC cohort who are 15-16 years old and live in the metro area of Minneapolis and St. Paul to be involved in this study of the etiologic factors of obesity in adolescents. We will assess potential obesogenic factors at the individual, family, school and community level by collecting data at three time points over a period of 24 months. Individual measures will include anthropometry and a variety of psychosocial, preference and behavioral assessments related to eating and activity. Family measures will include family socioeconomic status, parent weight and body composition, family meal and activity patterns, and the home food and activity environments. School level measures will include opportunities for physical activity, competitive foods, and school food and activity policies. Community-level measures will include the use of Geographical Information System (CIS) to assess obesogenic environmental factors such as the presence of walking and bike paths, convenience stores, and fast food restaurants. This research is multidisciplinary involving researchers from across four departments at the University of Minnesota (the Division of Epidemiology, School of Nursing, School of Kinesiology, and the College of Architecture and Landscape Architecture) and including scientists with a expertise in the biological sciences, exercise physiology, nutrition, the behavioral sciences, psychology, and urban planning. This research proposal is intended to be the first in a series of proposals that will include following the cohort into young adulthood to

assess obesity risk and related cancers, help in directing the focus of future interventions to prevent the onset of childhood overweight and obesity in order to reduce chronic disease risk.

Project 2: Household Environmental Weight Gain Perspective
Principal Investigator: Simone French, PhD

Obesity is a national epidemic that is widely recognized to be environmental in origin, Primary prevention interventions that address both environmental and individual-level influences on obesity are urgently needed.

The primary aim of the proposed study is to evaluate a household-level weight-gain prevention intervention that includes both environmental change and individual-level behavior change components. Four hundred forty households will be recruited and randomized to one of two groups for a 1-year period: 1) household environmental weight-gain prevention program or 2) control program that provides only general behavioral weight control recommendations The primary outcome is household-level change in body weight over the 1-year intervention period.

The household environmental weight-gain prevention program includes reduced access to television viewing via a television time-limiting device; reduced household availability of high fat/energy prepackaged foods and less frequent fast food restaurant use; and increased frequency of self-weighing with the provision of a home scale to each household. In addition, the individual-level behavioral change component targets specific eating and exercise behaviors that dovetail with the household environmental changes to promote weight control.

The intervention program format consists of 6 monthly face-to-face group meetings, 12 monthly newsletters, 6 encouragement telephone calls, and continuous access to intervention staff via telephone and email. The control group program consists of 12 monthly newsletters that provide general behavioral recommendations for weight control.

The primary outcome is household-level percent weight change measured one year following the initiation of treatment. Secondary outcomes are changes in energy intake, physical activity, television viewing time, and frequency of self-weighing. It is hypothesized that intervention households will gain significantly less weight over the 1-year intervention period than households randomized to the control group.

Project 3: Women in Steady Exercise Research (WISER)
Principal Investigator: Mindy Kurzer, PhD, MS

It is not feasible to conduct randomized controlled exercise intervention trials with breast cancer diagnosis as the primary outcome. Therefore, it is of interest to determine whether exercise will alter physiologic outcomes associated with breast cancer incidence, including oxidative stress, estrogens, estrogen metabolism, and metabolic factors such as body fat, elevated fasting insulin, insulin resistance, alterations in plasma levels of IGF-axis proteins. We propose to examine the effects of aerobic exercise training on each of these mechanisms among young (18-30 years), pre-menopausal, eumenohrreic women in a randomized controlled trial. The primary hypothesis to be tested is whether exercise alters oxidative stress as measured by F2-Isoprostanes. The innovation of this grant stems from the concurrent measurement of cancer biomarkers, which will enable us to explore relationships between changes in these physiologic parameters that may have an important role in the exercise - cancer link. Compelling preliminary data indicate that the amount of exercise recommended for health promotion and chronic

disease prevention (5 weekly 30 min sessions of moderate intensity aerobic exercise) may alter these risk factors in a manner consistent with reduced cancer risk. We will recruit 400 women and anticipate a dropout rate of 20%, for a final sample of 320 women (n=160 per group). Measurements will be made from days 7 to 10 of the participants menstrual cycle prior to randomization and at the 5th menstrual cycle after the baseline cycle. Participants will also use ovulation kits to determine whether exercise alters luteal phase length or ovulatory status. Measurements will include oxidative stress (F2-isoprostanes), estrogen metabolites, body composition (dual energy x-ray absorptiometry), insulin, glucose, and insulin resistance (HOMA index), insulin-like growth factor axis proteins (IGF-1, IGFBP-1, -2, and -3), submaximal fitness, questionnaires (injury/illness, demographics), and diet (by food frequency questionnaire).

University of Southern California
Principal Investigators: Michael Goran, PhD and Leslie Bernstein, PhD

The University of Southern California TREC Research Center explored the physiological, metabolic, genetic, behavioral, and environmental influences on obesity and cancer risk in minority children. Overall Aim: We seek to establish a trans-disciplinary center to address the physiological, metabolic, behavioral, genetic, and environmental influences on obesity, metabolic health and cancer-risk with a focus on minority children. Leadership & Organization! The Center will be Directed by two distinguished and internationally known investigators in obesity, and cancer research (Michael I Goran, PhD &. Leslie Bernstein, PhD). Drs. Goran and Bernstein will lead a coherent and synergistic program of 3 Projects, 2 Pilot Studies, 3 Research Cores, and a Training Core, each led by collaborative teams of investigators from diverse disciplines. Projects: In Project 1, we will examine ethnic differences in obesity-related metabolic risk factors for cancer in Hispanic and African American youth and the potential role of strength training as an innovative intervention for improving these risk factors. Project 2 will examine the biological and behavioral basis for the decline in physical activity during puberty in minority girls. Project 3 will examine the "built" environment and urban sprawl as risk factors for the development of obesity in children. The 2 pilot studies will: 1) develop and pilot test a community-based obesity intervention for Hispanic youth; and 2) examine the contribution of obesity to DNA methylation in the colon. Cores: An Administration Core will provide scientific leadership and oversight, and provide opportunities for new collaboration and dissemination of findings. The research studies will be supported by a Data Management and Analysis Core, and a Human Measures Core. Finally, a Training and Career Development Core will support the next generation of trans-disciplinary investigators in obesity and cancer research. Summary & Significance: We envision this application as an unprecedented opportunity to harness the vast scientific expertise at the University of Southern California. The broad trans-disciplinary theme will encompass studies of novel mechanisms that span from the patient bedside to the community curbside, so that more effective interventions in childhood and adolescence can be developed. Our overall vision is based on the concept that preventing obesity and promoting health in children will improve long-term cancer control in the population.

Project 1: Obesity-Related Metabolic Risk for Cancer: Ethnicity and Response to Exercise in Minority Youth
Principal Investigator: Michael Goran, PhD

Overall Goal: Project 1 will determine ethnic differences in body fat distribution, insulin resistance, insulin-like growth factors and binding proteins, inflammatory markers and oxidative stress in overweight African American and Hispanics children during the critical period of adolescent growth. Thereafter, we will examine the impact of strength training as a therapeutic intervention to improve these risk factors. We build upon previous work to hypothesize that hyperinsulinemia in African American youth is associated with important metabolic differences that could increase long-term cancer risk. Specific Aims: (1) To determine the contribution of body fat compartments (visceral fat, muscle fat and liver fat) and adipokines to insulin resistance in African American and Hispanic youth; (2) To examine differences in metabolic compensation to insulin resistance between African American and Hispanic youth; (3) To examine the influence of body fat, insulin resistance and ethnicity on markers of lipid peroxidation and oxidative stress, and (4) To determine the effects of a randomized strength training intervention on potential mechanistic factors linking obesity to cancer risk. Design: Cross-sectional (40 African-Americans vs 40 Hispanics) and 16-week strength training program in which obese adolescents are randomly assigned to nutrition education or nutrition education plus supervised strength training. Dependent Variables: Major outcome variables include: Insulin sensitivity and

insulin response to glucose by intravenous glucose tolerance test; whole body composition by (dual energy X-ray absorptiometry); visceral fat, liver fat and muscle fat by magnetic resonance spectroscopy; blood draws for measures of oxidative stress, lipid peroxidaton, plasma lipids and genetic admixture; physical activity by accelerometry. Significance: Project 1 will shed new light on differences in metabolic risk factors for cancer between African Americans and Hispanics as well as their response to strength training. The contrast between African Americans and Hispanics is of particular interest because these groups share similar pre-disposition to obesity, greater insulin resistance and risk for type 2 diabetes, but for the major types of cancer, African Americans have substantially greater risk than Hispanics. Furthermore, this study will provide new information regarding the impact of strength training as an anti-obesity and anti-carcinogenic intervention in "at risk" minority adolescents.

Project 2: Insulin Resistance and Declining Physical Activity Levels in African-American and Latina Girls
Principal Investigator: Donna Spruijt-Metz, PhD

Overall goal: To determine physiological and psychological determinants of the decline in physical activity in Latina and African American girls during puberty. Rationale: The decline in physical activity that occurs during adolescence has been found consistently across gender, ethnicity and nationality in human studies, and across species in animal studies, suggesting a biological basis. The pubertal transition in Latina and African American girls represents a "critical period" of development in which increased insulin resistance and decreased physical activity have been noted. These "risky" metabolic and behavioral changes in this susceptible ethnic group may explain, in part, their increased risk for obesity. This pubertal decrease in physical activity also raises future risk of breast, endometrial and colon cancer. Specific aims and Approach: Aim 1 (Longitudinal Study): To determine the direct impact of pubertal insulin resistance in Latina and African American adolescent girls on physical activity, mood and meanings of physical activity across the pubertal transition from Tanner Stage 1-3. Aim 2: Tc determine how the impact of puberty induced insulin resistance on physical activity is mediated by moot and meanings of physical activity. Aim 3: To investigate ethnic differences in the impact of insulin resistance on mood, meanings of physical activity and physical activity. We will recruit 50 Latina girls and 50 African American girls 9-11 years of age at Tanner Stage 1. Yearly metabolic evaluations and quarterly accelerometry and psychosocial evaluations will be completed for a period of three years. A combination of path models and growth curve models will be used to understand the longitudinal impact of pubertal insulin resistance on mood, motivation and physical activity levels in Latina and African American girls as they mature. Central hypotheses: Pubertal insulin resistance leads to a decline in physical activity. The decline in physical activity in girls is partially biologically programmed, emanating from the "trigger" of insulin resistance, which is linked to affective determinants of physical activity including mood and energy levels, and these metabolic and psychological changes contribute to the marked decline in physical activity that occurs during puberty. This study will be the first to examine the temporal relationship between pubertal insulin resistance and the sharp decline in physical activity experienced by Latina and African American girls during puberty.

Project 3: Influence of Built Environments on the Development of Obesity During Childhood
Principal Investigator: Michael Jerrett, PhD

Background: Growing evidence now links the built environment to physical activity, dietary quality, and obesity. The goal of this study is to assess the influence of the built environment on longitudinal changes in body mass index (BMI) in a cohort of 11,797 children from 16

communities across Southern California. This study will focus on the contributing role of neighborhood-level factors to the progression toward overweight and obesity or "obesogenic trajectories". We define these trajectories as the temporal progression toward overweight and obesity compared to age-adjusted growth curves for the cohort.

Methods: We build on over 8 yrs of measurements on 6,259 children in the DSC Children's Health Study (CHS) (ages 9-10 at enrollment, reaching 18 years at end of follow up). We will supplement this data set with 4+ years of follow up on 5,538 children in a new cohort (ages 6-7 years at recruitment with follow up until they are 11-12 years). Participants have been thoroughly characterized with annual measurements of height and weight, lung function, physical activity, baseline dietary intake, gender, race, ethnicity, and socioeconomic status (SES). CHS data will be integrated with measures of the built environment derived in a Geographic Information System. We will test the impact of the built environment and obesogenic trajectories using spatial statistics and multilevel growth curve models.

Specific Aims: (1) To assess the effects of the neighborhood built environment on obesogenic trajectories and (2) To explore whether individual (i.e., gender, race, SES) and contextual variables (i.e., air pollution) modify the association between the built environment and obesogenic trajectories.

Significance: Specific strengths of this application include the examination of the effects of the built environment on children's prospective change in weight status, direct assessment of children's weight status annually, efficient use of existing environmental and individual data, and the ability to evaluate potential differential effects across ethnicity/race on the relation between built environment and obesity. This project will identify specific variables in the built environment that significantly influence the development of obesity in children. These findings could have public health implications with respect to structuring the built environment to prevent obesity in children.

Coordination Center- Fred Hutchinson Cancer Research Center
Principal Investigator: Mark Thornquist, PhD

Understanding the association between energetics and cancer risk, determining its underlying mechanisms, and developing effective interventions to alter energetics to decrease cancer risk are of paramount importance in reducing cancer risk in the U.S. in the face of a rising obesity epidemic. The study of energetics and cancer requires a transdisciplinary approach to transform knowledge obtained in the laboratory and epidemiological studies into interventions that work. The charge of the Transdisciplinary Research on Energetics and Cancer (TREC) consortium is to create a cross-disciplinary team of investigators to comprehensively deal with all aspects of the energetics and cancer in order to help NCI reach its year 2015 goal of eliminating suffering and death due to cancer. The TREC Coordination Center (CC) will facilitate the transformation of knowledge among the TREC Centers and the research community at large to enhance the pace of scientific progress and help ensure that the TREC consortium is greater than the sum of its parts.

Toward this end, under the direction of the TREC Steering Committee, the CC will

1) enhance scientific interactions by identifying research commonalities across TREC sites, developing common data elements and instruments, facilitating the mapping of existing data to the common elements, training investigators as needed, and creating a data warehouse for use by both the TREC Centers and the research community;

2) support communication and dissemination of knowledge through a web site, mailing lists, organizing meetings, and creating special working groups as needed; and

3) assist the NCI program office in developing evaluation metrics to measure the TREC consortium's progress.