TREC Overview

The Transdisciplinary Research on Energetics and Cancer (TREC) initiative is a major scientific research effort aimed at reducing cancer linked with obesity, poor diet, and low levels of physical activity.

The National Cancer Institute (NCI) established the TREC initiative in 2005 in response to growing public health concern with overweight and obesity in the United States and mounting evidence that obesity plays a role in the development of many types of cancer.

The relationships between obesity, energy balance, nutrition, physical activity, and cancer risk are highly complex. Finding answers to complex questions about obesity and cancer requires a transdisciplinary research approach where scientists from diverse fields come together to integrate knowledge across disciplines. The TREC initiative helps scientists conduct transdisciplinary research on obesity and cancer and also helps train new and established scientists to carry out this kind of integrated research. The TREC initiative complements NCI's energy balance research endeavors and efforts of the NIH Obesity Task Force.

In 2005, NCI funded the first four TREC Research Centers and one Coordination Center. The centers included scientists from multiple disciplines and encompassed projects spanning the basic biology and genetics of behavioral, socio-cultural, and environmental influences on nutrition, physical activity, weight, energy balance, energetics, and cancer risk. The Coordination Center facilitated interactions across and between the Research Centers and the NCI. In the first five years of funding, fourteen research projects and several developmental pilot projects were supported and a transdisciplinary infrastructure to promote research collaborations in the area of energy balance and cancer was established. The first five years of funding for TREC ended in September 2010.

In 2011, NCI announced the four newly awarded TREC Research Centers and continuation of the Coordination Center. The overall purpose of the current TREC initiative is to foster transdisciplinary research in nutrition, physical activity, energy balance, and cancer. As in the first five years of funding, the current TREC initiative continues to emphasize collaboration across diverse disciplines such as behavior science, physiology and metabolism, sociology, communications, geography, psychology, kinesiology, nutrition, biostatistics, biochemistry, molecular biology, and other diverse disciplines.

The current TREC initiative expands into other research areas including cancer survivorship, childhood obesity, genomics, and environmental aspects of obesity that include use of tools such as geospatial analysis. The current program also includes additional emphasis on testing and integrating behavior change theories, challenges in survivor populations, systems analysis, using animal and human studies in diverse research designs, and expansion of the application of biological markers to inform behavioral-based research. Training new and established scientists to carry out transdisciplinary research continues to be a part of the current TREC initiative.

What is transdisciplinary research?
Transdisciplinary research is defined as research efforts conducted by investigators from different disciplines working jointly to create new conceptual, theoretical, methodological, and translational innovations that integrate and move beyond discipline-specific approaches to address a common problem.

What is energetics?
Energetics in the context of the TREC initiative is defined as the study of the flow and transformation of energy through living systems (i.e., bioenergetics).

What is energy balance?
The term energy balance refers to the integrated effects of diet, physical activity, and genetics on growth and body weight over an individual's lifetime.

TREC's Vision, Mission & Values

- Vision: Energizing science and society to combat obesity and cancer.

- Mission: Our goal is to integrate diverse disciplines to find effective interventions across the lifespan to reduce the burden of obesity and cancer and to improve population health.

- Broad Strategies:
  - We do this by building teams who create sustainable solutions to address a complex problem from geography to genes.
  - We engage and inspire the next generation of scientists to embrace transdisciplinary research in energetics and cancer.

- The core values we share:
  - fostering collaborations AND healthy competition
  - sharing our ideas across sites makes our science better
  - ensuring everybody has a voice
  - building trusting relationships with each other
  - valuing many types of expertise
  - everyone bringing their best to the table
  - creating a safe environment that facilitates getting people out of their comfort zones

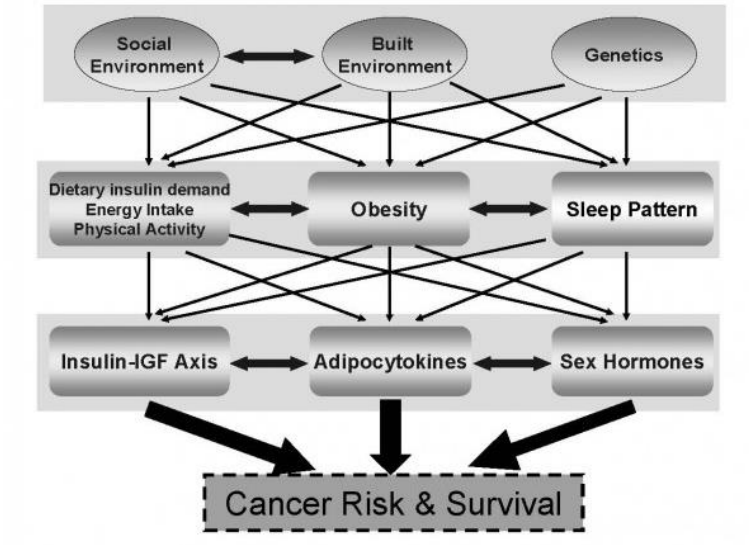
Harvard University
Principal Investigator: Frank Hu, M.D., Ph.D., M.P.H.

The Harvard TREC Center is a NCI-funded research center focused on investigating the relationship between obesity and cancer by integrating the study of diet, weight, and physical activity and exploring these effects on energy balance and cancer incidence and survival. The Center draws on the multidisciplinary expertise of the faculty of the Harvard School of Public Health, the Harvard Medical School, the Harvard-affiliated Brigham and Women's Hospital, Children's Hospital Boston, Dana-Farber/Harvard Cancer Center, Harvard Pilgrim Health Care Institute, Massachusetts General Hospital and the Harvard Center for Population and Development Studies. The Center is designed to increase the understanding of the determinants of obesity from the molecular to societal level and across the lifespan, to clarify the biological links of obesity with cancer risk and survivorship, to translate these findings into actionable behavioral interventions, to train the next generation of investigators in energetics (the study of energy balance) and cancer, and to disseminate this knowledge and develop public health strategies to reduce risk of obesity and cancer.

Conceptual Framework & Life Course Approach

The conceptual model for the Harvard TREC research projects is illustrated in Figure 1 below. This multilevel model posits that macro-level and energetic factors influence cancer risk and survival through multiple interrelated pathways, with cancer-related biomarkers (insulin/IGF components, sex hormones, and adipokines) at the *fulcrum point* in energy balance and cancer pathophysiology. As a whole, the four primary projects address how genetic, behavioral, and structural factors influence obesity and the biologic mediators between obesity and cancer at multiple stages of life (infants, adolescents, healthy adults and cancer survivors), how these determinants interact with each other, and, ultimately, whether these biologic mediators influence cancer survival and are modifiable among cancer survivors. The projects also use a variety of research strategies including the combination of qualitative and quantitative methodologies in a contextual study, observational studies, behavioral and pharmacological interventions, and multilevel research to address the multiple levels of influence that genetic factors, circulating biomarkers, anthropometry, diet, behavioral factors, the social environment, and the built environment have on the proposed disease outcomes, their mediating effects, and interactions. Each project addresses both overlapping and distinct pieces of the puzzle of the determinants of obesity and the links between obesity and cancer risk and survival.

Figure 1. Harvard TREC Conceptual Model



Project 1: Childhood Sleep Patterns

Sleep duration, energy balance, and insulin resistance in children

This project is led by Elsie Taveras, MD, MPH, a pediatrician and epidemiologist whose clinical practice and research focuses on the prevention of obesity in children. In this project, Dr. Taveras is investigating the role of sleep duration and sleep patterns in early childhood as risk factors for obesity and metabolic dysfunction in adolescence.

The specific aims are:

- to examine the extent to which short sleep duration in infancy, chronic insufficient sleep from infancy to mid-childhood, and sleep duration and efficiency at age 11 years are associated with adiposity, fat mass distribution, metabolic syndrome, and cancer-related biomarkers
- to examine the extent to which these associations are mediated by dietary behaviors, the composition of diet, and physical activity/inactivity behaviors (e.g., television viewing)
- to examine the extent to which these associations are modified by genetic factors related to sleep duration and either insulin resistance or beta-cell function

Dr. Taveras uses data from *Project Viva*, a prospective pre-birth cohort study (birth to age 11 years) and the *Cleveland Children's Sleep and Health Study* cohort (ages 8 to 19 years) to provide information on sleep, behavioral risk factors, and obesity across the entire pediatric age span.

This project translates the results of observational studies into behavioral interventions and turns the research findings into theory-based behavioral interventions aimed at modifying sleep patterns during infancy and early childhood. This project will not only advance the current understanding of the long-term effects of sleep disorders during infancy and early childhood on body composition and metabolic function, but also will generate knowledge that can be immediately turned into action to prevent any long-term health consequences that abnormal sleep patterns might have on children. This project will also generate novel data on the moderating role of genetic variants that influence sleep and circadian rhythms in obesity and insulin resistance.

Project 2: Environmental and Lifestyle Factors

Environmental and lifestyle factors, obesity and cancer-related biomarkers

This project, led by Frank Hu, MD, PhD, examines the association of behavioral and environmental factors with circulating levels of cancer-related biomarkers among 750 middle aged women in the *Nurses' Health Study*, and evaluates whether selected genetic characteristics modify the associations between behavioral and environmental factors and risk of obesity.

The specific aims are**:**

- to examine associations between energetic factors (energy expenditure measured by doubly labeled water, physical activity, dietary insulin demand, and sleep duration) and cancer-related biomarkers (insulin/IGF pathway, adipokines, and sex hormones)
- to examine the relationships of neighborhood social economical status (SES) and built environment (assessed by the county sprawl index) with cancer-related biomarkers and delineate the pathways linking the built environment, energetic factors, obesity and biomarker levels
- to examine whether genetic factors related to insulin resistance or insulin secretion modify the associations between behavioral (dietary insulin demand, physical activity, and sleep duration) and structural (neighborhood SES and built environment) factors and risk of obesity and long-term weight gain. These analyses will be conducted among 8,000 participants with existing genome-wide association study (GWAS) data in the *Nurses' Health Study* and *Health Professionals' Follow-up Study*.

This project is designed to provide thematic continuity with project 1 in two regards: sleep patterns is one of the behavioral factors examined, and there is substantial overlap in the biomarkers (including insulin/IGF pathway and adipokines) examined as outcomes in Projects 1 and 2. The primary aims of this project are to investigate the relation of objectively measured energy expenditure, physical activity, and dietary insulin index/insulin load with the same biomarkers of cancer risk, to study the association between different aspects of the built environment and biomarkers of cancer risk, and to evaluate whether specific genetic variants modify how sleep, nutrition, and the built environment influence cancer-related biomarkers. This project will enhance our understanding of how multiple novel factors, from genes to geography, influence circulating levels of biomarkers of cancer risk on their own and by interacting with each other.

Project 3: Biologic Factors and Prostate Cancer

Energetics, fatal prostate cancer, and overall survival

The overall goal of this project, co-led by Jing Ma, MD, PhD, and Howard Sesso, ScD, is to gain a better understanding of the biological mechanisms linking obesity with prostate cancer survival, with a focus on biomarkers of the insulin/IGF pathway and adipocyte function.

The specific aims are**:**

- to investigate how adiposity assessed at multiple points during adult life, and type 2 diabetes, and the insulin/IGF metabolic pathway influence prostate cancer survival in the *Physicians' Health Study*
- to evaluate insulin/IGF metabolism, circulating biomarkers, genetic determinants, and dietary input at multiple levels, including pathologic conditions
- to examine whether the built environment also influences prostate cancer survival through its impact on physical activity and to delineate the pathways linking this macro-level variable to obesity, biomarker levels, and cancer survivorship
- This project investigates how geospatial and genetic variables are related to biomarker levels and prostate cancer survival allowing for thematic continuity across projects. We expect that findings of these studies will provide new insights into the role of energy metabolism in prostate cancer progression; will guide the identification of novel cancer therapeutic targets; and will help the development of cancer prevention strategies spanning urban planning, diet, and lifestyle modification.

Project 4: Exercise/Metformin and Colorectal and Breast Cancer Survivors

The impact of exercise and metformin on hyperinsulinemia in colorectal and breast cancer survivors

The primary goal of this project is to examine whether a behavioral intervention aimed at increasing physical activity and metformin, alone or in combination, can reduce the levels of fasting insulin in colorectal and breast cancer survivors. The project is co-led by Jeffrey Meyerhardt, MD, MPH and Jennifer Ligibel, MD at Dana-Farber Cancer Institute with collaboration from Lee Jones, PhD at Memorial Sloan Kettering Institute (previously at Duke University) and Melinda Irwin, PhD at Yale Medical School.

The specific aims are:

- to examine the individual and joint effects of these interventions on fasting insulin levels, C-peptide, IGF-1, inflammatory and other biomarkers of this metabolic pathway
- to assess change in body mass index
- to determine whether the theoretical constructs of planned behavior can predict change in exercise behavior in colorectal cancer survivors

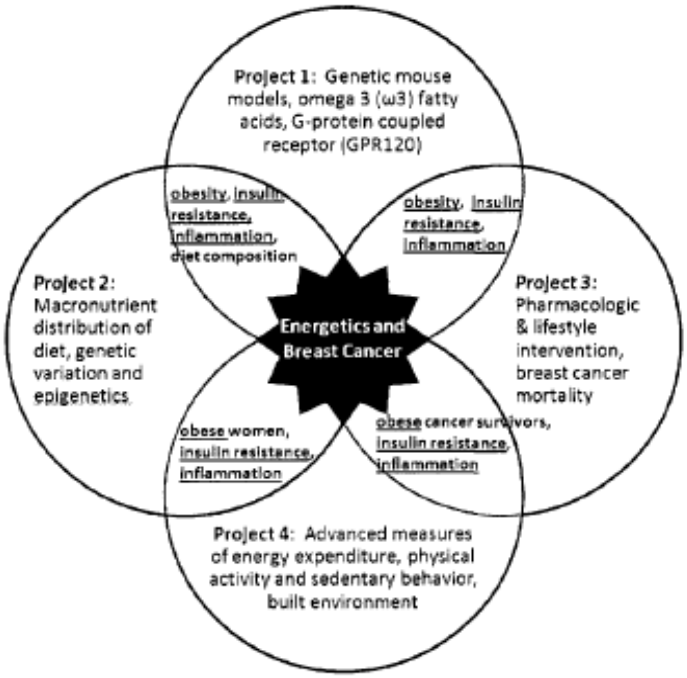
Observational evidence suggests that factors related to energy balance, including exercise, body weight and diet, may be related not only to the risk of developing colorectal and breast cancer, but also to prognosis in patients who develop the disease. Several studies have demonstrated that colorectal and breast cancer risk and recurrence rates are elevated in individuals with higher circulating levels of insulin or C-peptide as well as in individuals with higher levels of insulin-like growth factor (IGF)-1 or lower levels of IGF binding protein (IGFBP)-3. However, there are no data testing strategies to lower levels of insulin or related hormones in colorectal and breast cancer survivors. Two strategies that have strong scientific rationale to impact the insulin-related pathways are exercise intervention and metformin. This project explores these strategies through a multi-site clinical trial.

University of California, San Diego
Principal Investigator: Ruth Patterson, Ph.D., M.S.

The objective of the University of California San Diego (UCSD) TREC Center is to enhance knowledge of the role of insulin resistance and inflammation, from the cell to the community, underlying the association between energetics and breast cancer. This Center also explores and integrates the etiology of obesity and relevant health behavior theories, with broad population impact at the social-environmental and policy levels for prevention and control of obesity.

The overall approach of this Center is to leverage transdisciplinary, innovative, and rigorous scientific approaches to enhance our understanding of energetics and breast cancer. As illustrated in Figure 2, there considerable is overlap among the four UCSD TREC research projects (see detailed project descriptions below). In particular, obesity, insulin resistance, inflammation, and breast cancer and are shared research themes across all the projects. The studies articulate the gaps in knowledge addressed by these research efforts and are hypothesis driven. All studies use rigorous experimental designs (e.g., randomized trials) and objective measures of lifestyle (e.g., measured weight loss, accelerometers, heart rate monitors). These studies include mouse models, obese women, breast cancer survivors, and the community.

Figure 2. Relationships Among the UCSD TREC Research Projects:
Project 1. Role of Inflammation in Insulin Resistance in Mouse Models of Breast Cancer, Project 2. Diet Composition and Genetics: Effects on Weight Inflammation and Biomarkers, Project 3. Obesity-Related Mechanisms and Mortality in Breast Cancer Survivors, Project 4. Advancing Assessment of Energy Expenditure in Women with Increased Cancer Risk



Project 1. Role of Inflammation and Insulin Resistance in Mouse Models of Breast Cancer.
Principal Investigator: Jerrold Olefsky, MD

Obesity confers increased risk for various forms of cancer. Breast, colon, and liver cancer are all increased in obese populations and the epidemiologic evidence for the obesity - breast cancer connection is compelling. One in eight women will be diagnosed with breast cancer during her lifetime. Breast cancer is strongly associated with age as incidence increases 10-fold for women age $\geq$ 60 compared to women age $\geq$ 50. Increased risk with age seems related to post-menopausal hormone levels as both obesity and hyperinsulinemia are associated with increased breast cancer risk only in women not on hormone replacement therapy. Metabolic Syndrome is associated with a higher incidence of aggressive triple negative breast tumors (ER-/PR-/HER2-) which is likely accelerated by ovarian hormone decline

after menopause, as post-menopausal women are more susceptible to the deleterious metabolic effects of obesity including chronic inflammation and insulin resistance. Rodent studies have confirmed this relationship, showing that diet-induced obesity and high fat diets lead to increased incidence and growth of tumors in various breast cancer models. Despite this body of correlative evidence, the mechanisms of obesity-induced breast cancer risk remain poorly understood. Diet composition is an important factor as diets rich in saturated and omega 6 fatty acids (FAs) are pro-inflammatory and increase breast cancer risk, but diets rich in omega 3 FAs are anti-inflammatory and decrease cancer risk. The clinical data is less clear but meta-analyses of multiple human breast cancer risk studies suggest that the ratio of omega 6 to omega 3 FAs is a critical factor.

We have found that the beneficial anti-inflammatory and insulin-sensitizing effects of omega 3 FAs are mediated by the G-protein coupled receptor GPR120. Due to the potential link between obesity, insulin resistance and breast cancer risk in post-menopausal women, we hypothesize that GPR120 is the critical mediator of the protective effects of omega 3 FAs in breast cancer. We are testing this in four specific aims that combine 1) studies using orthotopic tumor cell transplants and 2) spontaneous tumors in obese wild type (WT) and GPR120 knockout (KO) mice, ± omega 3 FA supplementation, 3) studies using orthotopic mouse and human tumor cell transplants into RAG2 KO mice, and 4) studies of metastasis using genetically marked tumor cells in obese WT and GPR120 KO mice. We hypothesize that omega 3 FAs will attenuate tumorigenesis and metastasis in WT but not GPR120 KO mice through their anti-inflammatory/insulin-sensitizing actions. This project aims to provide mechanistic depth that is complementary to aims of Projects 2 & 3.

Project 2. Diet Composition and Genetics: Effects on Weight, Inflammation and Biomarkers. [MENU STUDY].
Principal Investigator: Cheryl L Rock, PhD, RD

Excess adiposity is a risk factor for postmenopausal breast cancer and a major risk factor for recurrence in both pre- and postmenopausal breast cancer, and the biological mechanisms are not fully understood. Obesity is associated with elevated endogenous circulating estrogen as well as activation of the immune system, a key causative factor in insulin resistance and hyperinsulinemia. Optimal macronutrient distribution of weight loss diets has not been established. Cancer control guidelines have historically encouraged a low fat diets, but current evidence does not suggest this strategy to be of particular benefit. Emerging evidence suggests that the optimal diet composition for weight loss may differ across individuals based on metabolic status and genetic factors. Effects of diet composition on hormonal and other factors linking obesity to breast cancer in weight loss interventions have not been compared or examined.

The specific aims of this study are: (1) To examine whether there is a differential weight loss response to different dietary macronutrient composition in weight loss intervention in healthy obese women, depending on insulin resistance status; (2) To examine whether there is a differential response (depending on insulin resistance status) to different dietary macronutrient composition in a weight loss intervention in the hormonal factors and markers of inflammation that may link obesity to breast cancer mortality (insulin, SHBG, estrogens, C-reactive protein, interleukin-6 [IL-6], tumor necrosis factor a [TNF-a], and as a marker for gene expression, IL-6 and TNF-a gene methylation); and (3) To identify nutrient-gene interactions that contribute to differential response of cytokines to weight loss and diet composition associated with polymorphisms in IL-6 and TNF-a genes.

These aims are addressed in a randomized controlled study involving 156 obese women randomly assigned to a high-carbohydrate (65% energy) low-fat (20% energy) or low-carbohydrate (45% energy) high monounsaturated fat (35% energy) diet in a 12-month behavioral weight loss program. We hypothesize that greater weight loss and reduction in biomarkers will occur in insulin resistant women assigned to the lower carbohydrate, higher fat diet. We also hypothesize that the ability of weight loss and diet modification to decrease IL-6 and TNF-a concentrations will be influenced by polymorphisms in these genes. Results of this study will help to refine and individualize dietary guidance for optimal weight control and breast cancer prevention and will contribute to knowledge of mechanisms that link insulin resistance, inflammation and obesity to risk and progression of breast cancer.

Project 3. Obesity-Related Mechanisms and Mortality in Breast Cancer Survivors. [REACH FOR HEALTH STUDY].
Principal Investigator: Ruth E. Patterson, PhD

The objective of this study is to investigate the degree to which metformin, a lifestyle intervention, or both, can reduce breast cancer mortality among overweight/obese, postmenopausal breast cancer survivors. We use a "Biomarker Bridge" design that links clinical outcomes from a breast cancer survivor cohort with intermediate outcomes from a randomized controlled trial by means of a Biomarker Risk Score. Biomarker Risk Score Development: We are assaying panels of interrelated biomarkers in 375 archived blood samples obtained from overweight/obese, postmenopausal women with a history of breast cancer (125 cases [breast cancer death]:250 matched controls). These Biomarkers represent proposed mechanisms by which obesity is associated with postmenopausal breast cancer: (1) alterations in the insulin-IGF axis, (2) concentrations of endogenous sex hormones, and (3) chronic inflammation. We will identify a set of markers that best predicts breast cancer mortality using conditional logistic regression models adjusted for prognostic factors. This model (i.e., Biomarker Risk Score) measures the log-odds of disease risk due to joint biomarker concentrations. Therefore this Risk Score can measure changes in log-odds due to changes in these markers in an individual and will be used to assess the clinical impact of the metformin and lifestyle intervention randomized trial.

Metformin/Lifestyle Intervention Trial: We are conducting a 6-month, randomized controlled trial in 340 overweight/obese, postmenopausal breast cancer survivors. Participants are randomized in equal numbers to (1) placebo, (2) metformin, (3) lifestyle intervention and placebo, or (4) lifestyle intervention and metformin. The lifestyle intervention will focus on reducing energy intake and increasing energy expenditure to achieve a 7% weight reduction. Biomarkers that compose the Risk Score will be assayed in fasting blood samples collected at baseline and 6 months. The degree to which each intervention changes (e.g., reduces) the Biomarker Risk Score will be used to predict changes (e.g. reductions) in breast cancer mortality. We hypothesize that metformin and lifestyle interventions will reduce breast cancer mortality and that the combination of those interventions will have an additive effect on lowering risk.

In summary, this Biomarker Bridge Design will (i) develop a Biomarker Risk Score that predicts breast cancer mortality, (ii) examine how a metformin/lifestyle intervention changes this Risk Score, and (iii) thereby assess the degree to which metformin and lifestyle interventions influence the biological processes linking obesity with breast cancer mortality.

Project 4: Advancing Assessment of Energy Expenditure in Women with Increased Cancer Risk.
Principal Investigator: Jacqueline Kerr, PhD

Energy expenditure is a key component of energetics, and physical activity comprises the largest modifiable component of energy expenditure. Energy expenditure and physical activity are strongly related to Insulin resistance and other markers of glycemic control important for cancer risk. Sedentary behavior has also recently emerged as an independent predictor of metabolic risk, and temporal analyses of objective sedentary behavior data have indicated that breaks in sitting time may be a critical intervention strategy to complement improvements in moderate to vigorous physical activity. In the last decade, the impact of the built environment has also been assessed in relation to physical activity, sedentary behavior and weight status. This research, however, has focused on a static view of residential neighborhoods which may be confounding the relationship between health and place.

This study advances the field of energy expenditure, physical activity, and sedentary behavior assessment across the cancer continuum by improving the accuracy of energy expenditure-related assessments in our TREC projects #2 and #3. We are using state-of-the-art accelerometers with simultaneous heart rate recording to improve the accuracy of measuring physical activity, sedentary behavior, and energy expenditure. In addition to branched equation modeling techniques we also use new computational approaches for analyzing data streams from these devices, including artificial neural networks that allow combining these data to decipher the frequency, intensity, duration, and type of physical activity and sedentary behavior so as to optimally characterize behaviors of study participants and reduce the measurement noise in observed relationships between these behaviors and markers of glycemic control. Finally, data from Global Positioning System devices that track the temporal and spatial movements of participants is combined with existing Geographic Information Systems data for San Diego County to allow us to develop obesogenic environmental exposure estimates and relate these to the metabolic risk factors. These data are processed through software developed by our group under the NIH Gene & Environment Initiative. This enables us to use novel computational techniques to assess the relationships over time and across the study arms between energy expenditure, physical activity and sedentary behavior and metabolic risk factors related to breast cancer measured in Projects #2 and #3 as well as the moderating effect of exposure to obesogenic environments.

University of Pennsylvania
Principal Investigator: Kathryn Schmitz, Ph.D., M.P.H.

The central mission of the Penn TREC Survivor Center is to advance science on energetics and cancer survivorship, toward the goal of improving both the length and quality of cancer survivorship.

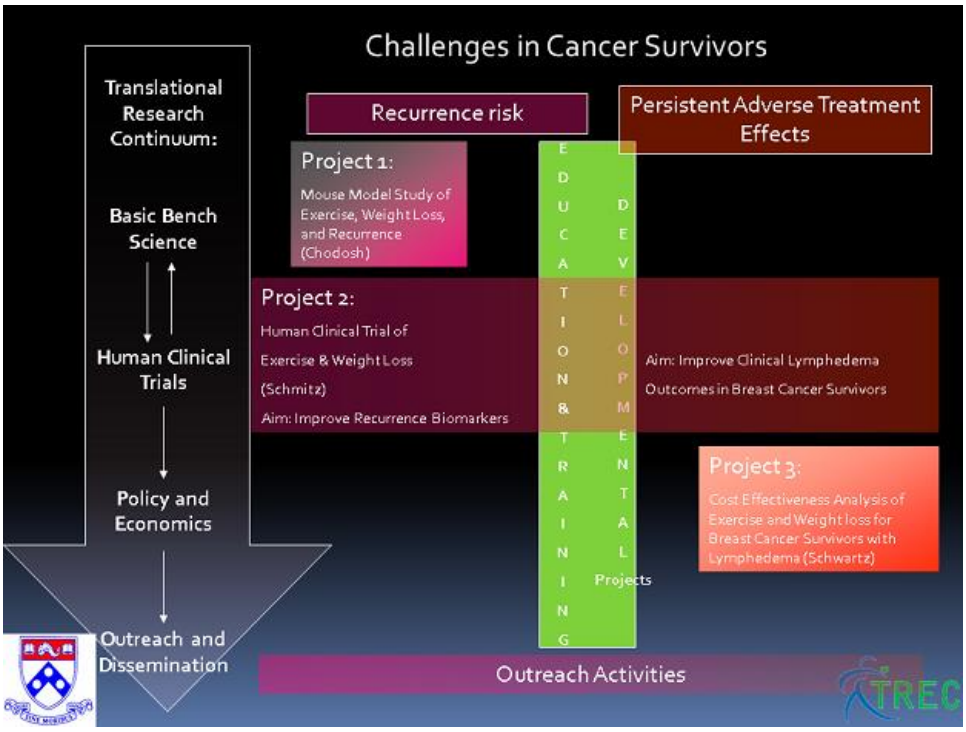
The Penn TREC Survivor Center includes three translational and transdisciplinary projects designed to support its central mission. Project 1 studies the effects of exercise and/or weight loss in mice; these data are used by Project 2 to study these same effects on female breast cancer survivors with lymphedema. Project 3 builds on Project 2 by analyzing the cost effectiveness of the exercise and/or weight loss intervention.

The energy balance issues facing cancer survivors are complex, underscoring the necessity of applying a transdisciplinary research model to improve outcomes. As such, the Penn TREC Survivor Center funds three projects that supports the following overall aims:

1. Conduct 3 inter-related Primary Projects aimed at understanding how exercise and/or weight loss alter risk for recurrence and improve clinical outcomes for a costly persistent long-term adverse effect of breast cancer treatment.
2. Provide overall coordination and facilitate transdisciplinary collaboration through an Administrative Core that provides administrative and budgetary oversight to the Center.
3. Accelerate research capacity through a Developmental Research Core that implements and supports innovative transdisciplinary pilot projects.
4. Create an Education/Training and Outreach Core that trains physician and non-physician researchers for careers in cancer survivorship and obesity research.
5. Support and integrate TREC research through a state-of-the-art Bioinformatics Core

<u>Conceptual Framework of the Penn TREC Survivor Center</u>
The conceptual model for the overarching vision of this Center is illustrated in Figure 3. On the left side, an arrow pointing downward depicts the translational research continuum, moving back and forth from basic bench science to human clinical trials, and onward to policy and economics, and ending with outreach and dissemination efforts. The Center addresses each level of this continuum within the primary projects and within education/training and outreach, and developmental pilot efforts. These activities are deeply transdisciplinary, including efforts from established investigators in the fields of epidemiology, cancer biology, mouse model development, health economics, physical medicine and rehabilitation, public health, dissemination research, clinical obesity treatment, exercise physiology, obesity bench scientists, biostatistics, clinical oncology, nuclear medicine, cellular and molecular biology, and health policy. The projects address both categories of major challenges faced by survivors: risk of recurrence and persistent adverse effects of treatment. Efforts are made to ensure that both types of challenges are addressed within education/training AND developmental pilot work as the center expands to include trainees and junior investigators training to become the new generation of scientists that can tackle obesity and cancer survivorship related research challenges. The considerable depth and breadth of obesity and cancer investigators at Penn extends from basic scientists to clinical trialists and health economists, including clinicians and non-clinicians. This is brought to bear toward our central mission of improving outcomes for cancer survivors.

Figure 3. Conceptual Model for the Penn TREC Survivor Center.



Project 1: The Impact of Exercise and Caloric Restriction on Cancer Recurrence in Mice
Key Personnel

- Lewis A. Chodosh, MD, PhD, Project Leader, Endocrinologist, Cancer Biologist
- Sandra Ryeom, PhD, Co-Investigator, Tumor Angiogenesis
- Joseph Libonati, PhD, Co-Investigator, Exercise Physiologist
- Rexford Ahima, MD, PhD, Significant Contributor, Endocrinologist

The goal of Project 1 is to advance our understanding of the impact of energetics on breast cancer recurrence. This project uses genetically engineered mice to determine the exercise, caloric restriction or both on breast cancer recurrence using a unique combination of strengths and expertise in cancer biology, obesity, endocrinology and exercise physiology at Penn.

Specific Aims:

1. Determine the effects of caloric restriction or exercise, alone or in combination, on the risk for breast cancer recurrence in overweight genetically engineered mice bearing minimal residual disease.
2. Evaluate the effects of these interventions on the carcinogenic process, including:
    - Circulating biomarkers
        - Insulin-IGF1 axis
        - Adipokines
        - Sex steroids
        - Inflammation
        - Oxidative stress
    - Biomarkers in recurrent tumors and minimal residual disease
        - Proliferation, apoptosis, angiogenesis

Project 2: The Women in Steady Exercise Research (WISER) Survivor Trial
Key Personnel

- Kathryn H. Schmitz, PhD, MPH, FACSM, Project Leader, Exercise Intervention Coordinator
- David Sarwer, PhD, Co-Investigator, Weight-Loss Intervention Coordinator
- Angela DeMichele, MD, MSCE, Co-investigator, Breast Oncologist

The goal of Project 2 is to assess the effects of exercise training and/or weight loss through caloric restriction on lymphedema, a common long term adverse effect of cancer treatment, biomarkers for recurrence and quality of life. This project was designed as a one year randomized controlled weight loss and exercise intervention trial in a multi-ethnic cohort of overweight and obese post-menopausal breast cancer survivors with lymphedema.

Specific Aims:

1. Assess the effects of one year of exercise, weight loss or the combined intervention on clinical lymphedema outcomes including incident events requiring medical care for lymphedema, arm swelling in the affected limb and pain and lymphedema symptoms.
2. Assess the effects of intervention on sex steroids, inflammatory markers, adipokines, oxidative stress, growth factors and pathogenic angiogenesis, a novel recurrence pathway.
3. Assess the effects of intervention on quality of life outcomes including lymphedema quality of life and body image.

Project 3: Breast Cancer Related Lymphedema: Cost of Illness and Cost Effectiveness of Alternative Management Strategies
Key Personnel

- J. Sanford Schwartz, MD, Principal Investigator, Project Oversight
- Andrea Cheville, MD, MSCE, Co-Investigator, Lymphedema and Rehabilitation Physician
- Daniel F. Heitjan, PhD, Co-Investigator, Biostatistician

The goal of Project 3 is to characterize the medical economic impact of breast cancer related lymphedema as well as short-term and long-term health consequences.

Specific Aims:

1. Assess direct medical care costs associated with management of breast cancer related lymphedema
2. Assess the cost-effectiveness and cost-utility of Project 2 interventions
3. Model the impact of Project 2 interventions over an extended time frame beyond that of the Project 2 RCT time

The projects and cores of the Penn TREC Survivor Center seek to accelerate capacity and refine existing research paradigms for research on energetics and cancer survivorship, toward the goal of improving outcomes in cancer survivors.

Washington University in St. Louis
Principal Investigator: Graham Colditz, M.D., Dr.P.H.

The Transdisciplinary Research on Energetics and Cancer (TREC) Center at Washington University in St. Louis (TREC@WUSTL) brings together a broad base of nationally and internationally recognized investigators in their disciplinary focus areas to lead transdisciplinary research across the life course on cancer and obesity. To accomplish this, the TREC@WUSTL:

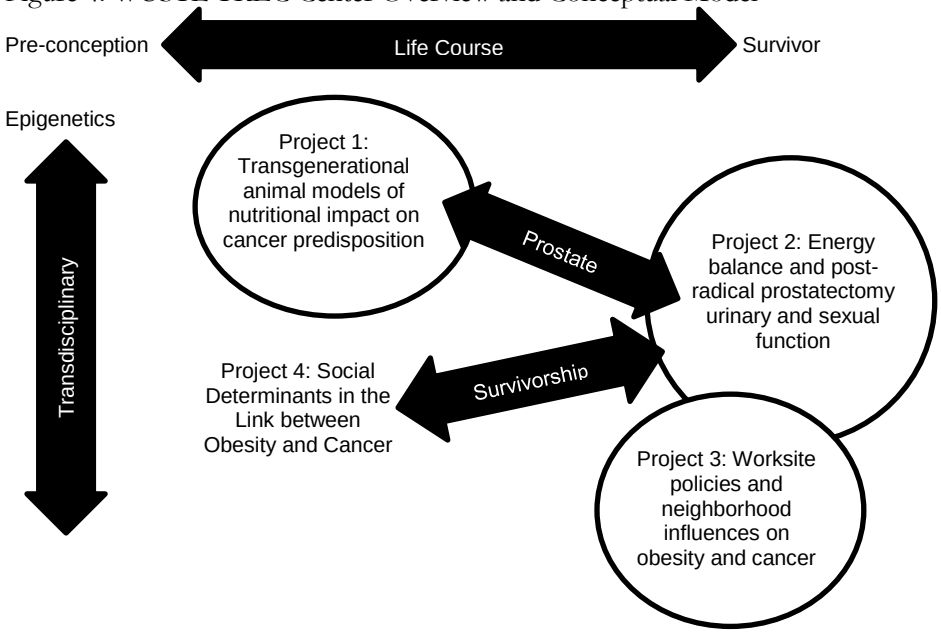
- Examines energetics from the molecular to the social/environmental level to understand cancer etiology
- Trains postdoctoral fellows in transdisciplinary research in a transdisciplinary environment to pursue careers in energetics and cancer
- Exposes scholars from across the university and region to transdisciplinary work in obesity and cancer
- Fosters scientific synergy via small-scale innovative transdisciplinary pilot projects that build on the TREC@WUSTL
- Uses five cores to support center research and close the gap between energetic and cancer scientific discovery and its application in clinical practice and population-based settings

TREC@WUSTL is fostered and supported by the Institute for Public Health, Washington University School of Medicine and the George Warren Brown School of Social Work. The center brings together broad scientific expertise from faculty within Washington University in St. Louis, and collaborators and consultants from other institutions, to study the relationship between obesity and cancer across the life course. This innovative transdisciplinary approach to cancer research moves beyond traditional risk factor associations to look at multilevel and multigenerational associations.

Through four research projects and five cores, TREC@WUSTL aims to answer the question: What are the factors in the molecular and social environments that influence energetics to produce cancer throughout the lifespan? This information will allow us to make recommendations for policy change to decrease rates of cancer and reduce the burden of cancer due to obesity. TREC@WUSTL also fosters transdisciplinary career development in obesity and cancer for postdoctoral fellows and scholars across our university.

<u>Overview and Conceptual Model of TREC@WUSTL</u>
With this Center's overall goal focusing on multilevel and multigenerational effects of obesity and physical inactivity and diet on cancer incidence, morbidity and mortality, TREC@WUSTL is significant in that it brings investigators from related fields into the study of cancer outcomes. It also moves investigators established in this area into collaborations that move their science beyond what it would have been in a stand-alone grant. We believe this attention to both high quality science and transdisciplinary research collaborations marks a significant advance. The result is Innovative science that has received scant attention in the cancer-energy balance field prior to TREC. Figure 4 provides a center overview.

Figure 4. WUSTL TREC Center Overview and Conceptual Model



Neighborhood

Project One
Transgenerational animal models of nutritional impact on cancer predisposition
Project Leader
Dr. Kelle H. Moley, James P. Crane Professor in Obstetrics and Gynecology, Division of Reproductive Endocrinology; Professor, Cell Biology and Physiology; Vice Chair and Director, Basic Science Research in Obstetrics and Gynecology

Collaborators
Dr. Adam S. Kibel, Professor of Surgery, Harvard Medical School; Chief of Urology, Brigham and Women's Hospital; and Chief of Urology, Dana Farber Cancer Institute
Dr. Jason Weber, Associate Professor of Medicine, Section of Molecular Oncology

Project Summary
Dr. Moley is looking at the effect of maternal high-fat diet and changes in metabolic bioenergetics on prostate gland development and susceptibility to prostate cancer in male offspring. This study addresses epigenetic changes that arise among offspring of obese females, leading to abnormal expression of key genes involved in the development of the prostate gland, which predispose the offspring to develop cancer. Dr. Moley's findings are positioned to inform molding of cancer in populations as implemented in Project Four.

Project Aims
1. Examine prostate gland development and imprinted gene expression in control *versus* high-fat fed offspring, from mothers given a high-fat diet one month prior to conception and throughout pregnancy.
2. Examine the incidence and timing of tumor development in offspring of control *versus* high-fat fed mothers by administration of diethylstilbestrol (DES) to neonatal male mice on postnatal days 1-5.
3. Examine the effects of a high-fat fed diet on tumor development in an established model for prostate cancers.

Project Two
PIE (Prostatectomy, Incontinence and Erectile function)
Project Co-Leaders
Dr. Graham Colditz, Chief and Niess-Gain Professor of Surgery, Division of Public Health Sciences, Department of Surgery, Washington University School of Medicine
Dr. Adam S. Kibel, Professor of Surgery, Harvard Medical School; Chief of Urology, Brigham and Women's Hospital; and Chief of Urology, Dana Farber Cancer Institute

Co-Investigator
Dr. Robert Grubb III, Assistant Professor of Urologic Surgery, Division of Urologic Surgery

Project Summary
This team is leveraging two existing cohort studies and will implement supplemental data collection to evaluate the role of physical activity and obesity in urinary and sexual function following surgical treatment for prostate cancer, thus addressing an important patient-driven outcome. Furthermore, this team addresses the TREC goal of expanding translational research to cancer survivors and evaluates potential differences in outcomes by race.

Project Aims
1. To determine the independent associations of pre-surgical physical activity (PA) and BMI on post-prostatectomy urinary and sexual function.
2. To explore the interaction of PA and BMI on urinary and sexual function.
3. To examine effect of change in PA and BMI from pre-surgery to 12 months post-op on urinary and sexual function.

Project Three
SHOW-ME Study (Supports at Home and Work for Maintaining Energy Balance)
Project Co-Leaders
Dr. Aaron Hipp, Assistant Professor, George Warren Brown School of Social Work
Dr. Ross Brownson, Professor, George Warren Brown School of Social Work

Co-Investigators
Dr. Elizabeth Dodson, Research Assistant Professor, George Warren Brown School of Social Work
Dr. Debra Haire-Joshu, Professor and Associate Dean for Research, George Warren Brown School of Social Work

Project Coordinator
Christine Marx, MA

Project Summary
This team addresses worksite environments and policies relevant for physical activity and diet behaviors and evaluates whether worksite supports for physical activity and healthy eating are predictive of obesity. Assessing worksite in the context of built environment will provide actionable knowledge about what policy changes in communities and worksites would have the greatest impact on healthy lifestyles to prevent obesity and related cancers. The investigators work with the Dissemination and Implementation Methods Core to bring their findings to local worksites, governments and practitioners.

Project Aims
1. Develop and test the reliability and validity of self-reported instruments for assessing worksite environments and policies relevant for physical activity and health eating.
2. Examine whether specific types and number of worksite supports for physical activity and healthy eating are predictive of obesity.
3. Examine whether perceived and objectively measured characteristics of the built environment in the home and worksite neighborhood are independently and jointly associated with BMI.
4. Disseminate findings to local worksites, governments and practitioners.

Project Four
Social determinants in the link between obesity and cancer
Project Co-Leaders
Dr. Peter Hovmand, Founding Director of the Social System Design Lab, George Warren Brown School of Social Work
Dr. Graham Colditz, Chief, Division of Public Health Sciences; Deputy Director, Institute for Public Health; Associate Director for Prevention and Control, Alvin J. Siteman Cancer Center

Co-Investigators
Dr. Kenneth Carson, Instructor, Medical Oncology Section
Timothy Hower, Associate Director, Social System Design Lab, George Warren Brown School of Social Work

Project Summary
This project focuses on understanding the role that social determinants play in the link between obesity and cancer at the population level across the lifespan. This team has developed a multi-cohort simulation model of obesity and non-Hodgkin's lymphoma (NHL). Additional cancers can be added to the model using data from this or other TREC Centers.

Project Aims
1. Develop a multi-cohort system dynamics computer simulation model of obesity and NHL population level outcome trends.
2. Analyze the resulting model to identify how social determinants influence obesity and NHL population level outcome trends.
3. Design guidelines along with their implementation strategies to identify the most effective way to reduce the impact of social determinants of NHL population level outcomes.

Coordination Center (FHCRC)
Principal Investigator: Mark Thornquist, Ph.D.

The overall aims of the TREC Coordinating Center are to: 1) facilitate transdisciplinary research through scientific leadership and organizational support with emphasis on efficient communication, coordination of efforts, and expanded scientific collaboration across multiple research institutions; 2) facilitate contacts between TREC awardees and NCI professional staff to allow for efficient interactions, consultations, and oversight functions; 3) create significant new opportunities for transdisciplinary training of scientists at every stage in their careers in the area of energetics and cancer; 4) create and manage relevant logistical infrastructure (including research data management and bioinformatics) to support the TREC Research Centers; 5) create opportunities to disseminate results across multiple venues; and 6) in collaboration with the NCI and the TREC Research Centers, facilitate integration and evaluation of TREC.

Under the direction of the TREC Steering Committee, the TREC CC 1) performs consortium coordination by providing support for TREC meetings and workshops, developing and maintaining TREC secure and public websites and electronic mailing lists, and producing and maintaining TREC documents; 2) supports TREC collaborative studies by offering the development and maintenance of collaborative study data management systems; 3) works with the NCI and the Steering Committee on evaluating TREC Centers and providing them constructive feedback; 5) works with the NCI and the Steering Committee to provide informatic resources for the sharing and dissemination of documentation and data; and 6) develops training programs to produce more transdisciplinary researchers in energetics and cancer. A sampling of the TREC CC's service offerings are listed in Figure 5.

Figure 5. Sampling of the TREC Coordination Center's Service Offerings by Core.

Core	Sampling of the TREC Coordination Center's Service Offerings Saves time and money for project teams within the TREC Centers
Leadership and Administration	Facilitate connections, collaboration, teams and networking Bring ideas forward across the consortium Scientific Meetings Coordination Facilitate communications and operational infrastructure for the consortium. We do this by: • Providing communications systems (TREC website, email distribution lists, etc) • Project management • Facilitating strategic planning • Team facilitation • Study coordination, including o Protocol coordination o SOP/procedures (coordinate development) o Regulatory guidance and support o Facilitate contracting / MTAs
Developmental Projects	RFA coordination and infrastructure Project management, study coordination support (see Leadership and Administration) Data collection & management (EDC services; user-authenticated, secured access, tailored to your study) Data harmonization and Common Data Elements (CDE) support Annually review, expand and update TREC studies "commonalities" document
Data and Bioinformatics	Centralize repository of data instruments Data capture, management, and analyses Pool and harmonize data elements across Centers Laboratory round robin Statistical support, methods consultation, training
Education, Training, and Outreach	Facilitate TD training and mentorship for early career investigators on the national level Coordinate and lead Educational Workshops Coordinate educational Webinars Manage and administer TREC's Knowledge Expansion and Education Program (KEEP) \

	Manage and administer TREC's Investigator Exchange Program Facilitate TREC research presentations at professional conferences Facilitate TREC involvement in relevant interest groups, expert panels
Integration and Self-Evaluation	Facilitate richness of understanding of integrated transdisciplinarity within and across TREC Centers CBPR methodology (engage community, empower stakeholders) Provide tools and resources for individual TREC Centers to integrate disciplines, knowledge, methods Provide broad perspective of the status and process of collaboration and transdisciplinarity in TREC
Other	Additional support may be available from the TREC CC, including: • Funding support for publication costs • Staffing support for conducting literature reviews • Other: Let us know what you need! We will consider helping in any ways that our staffing and resources allow.