Charles A. King Trust Postdoctoral Fellowship Program

Clinical and Health Services Research

2016 Grant Recipients

Franziska Plessow, Dr. rer. nat.
Massachusetts General Hospital
Mentor: Elizabeth Lawson, M.D., M.M.Sc.
"Cognitive Control as a Biomarker and Target for Novel Interventions in Low-Weight Eating Disorders"

Low-weight eating disorders (EDs) are characterized by extremes in food consumption and eating-related behavior, resulting in marked low weight. Their consequences are severe and often persist, and the illness onset is early with peak in the second decade of life, during a critical period of brain development. The pathophysiology of low-weight EDs, specifically the mechanisms determining restrictive eating versus restriction with binge/purging and differences in illness course, are mostly unknown. I hypothesize that alterations in cognitive control, the mechanisms that enable individuals to act on goals despite competing response tendencies, to flexibly adapt to environmental changes, and to prioritize long-term goals over short-term gains, represent a biomarker for adolescent low-weight EDs with distinct characteristics for different phenotypes and illness trajectories. In low-weight EDs, cognitive control processes and their neural pathways are markedly altered with findings indicating phenotype-specific profiles. Pilot data point toward an association between control alterations and symptom severity in adult ED patients. However, the prevalence of alterations in cognitive control in early disease stages and during adolescence as prime onset period and its relation to future clinical outcome is yet to be established. Using an innovative multi-component multi-level approach to cognitive control and leveraging an ongoing NIMH R01, I will characterize cognitive control competencies together with resting-state functional connectivity of the cognitive control network in 10-21 year-old females with restrictive eating and/or binge/purge behavior and healthy controls. I hypothesize that: (1) Altered cognitive control underlies patterns of restriction, binge eating, and purging, and differentiates low-weight ED patients from healthy, normal-weight controls. (2) Cognitive control abilities at baseline determine 4.5- and 9-month clinical outcome. This work aims to provide a systematic test of the predictive value of cognitive control profiles for phenotype and trajectory of low-weight EDs, identifying novel therapeutic targets to improve clinical care for this high-risk population.

Donald Robinaugh, Ph.D.
Massachusetts General Hospital
Mentor: Naomi Simon, M.D., M.Sc.
"Examining Symptom Decoupling and Propagating Causal Influence as Intra-individual Mechanisms of Change in Psychotherapy"

There is extensive evidence that many forms of psychotherapy are effective in treating a wide range of mental disorders. Yet, despite substantial advances in our understanding of what is effective, we know very little about how psychotherapies have their effect. In the proposed project, I will take a novel intra-individual network analysis approach to studying mechanisms of change complicated grief therapy (CGT), an empirically supported treatment for complicated grief (CG). According to the network approach, CG is a causal system of mutually reinforcing symptoms that arise together following the death of a loved one and settle into a pathological equilibrium. From this perspective, the symptoms are not passive diagnostic indicators of an underlying condition. Rather, they are active psychological variables that play a causal role in the maintenance of the disorder. Consequently, the symptoms themselves and the relations among them become potential targets for intervention and, thus, potential mechanisms by which treatments may have their effect. In the proposed study, I will conduct an open-trial of CGT and will use intensive time-series data and recently- developed intra-

individual network analyses to examine two plausible mechanisms of change by which CGT may have its effects: (a) a decoupling of the associations among CG symptoms and (b) propagating causal influence among CG symptoms in which reductions in symptoms central the CG network initiate a cascade of change that leads to reductions in overall CG severity. The findings from this study will identify mechanisms of change in CGT and, thereby, will allow for the development of new tools that better target those mechanisms as well as efforts to tailor interventions to target the processes most relevant to individual patients. In doing so, this study will pioneer a new method of examining and promoting change in psychotherapy for mental disorders.

2015 Grant Recipients

Jennifer Stevens, M.D.
Beth Israel Deaconess Medical Center
Mentor: Bruce Landon, M.D., MBA
"Inpatient Specialist Consultation: Understanding Drivers of Variation and Hidden Resource Use"

Inpatient consultation is the process of involving specialists in the care of a hospitalized patient, something which happens every two seconds in the United States. Despite its prevalence, very little research has explored this common physician practice. Our long-term research objective is to describe the multiple drivers of variation in the use of inpatient consultation, to understand the patient- and system-level value of this widely used exposure, and to develop interventions to measure and improve the quality of inpatient consultation. Our prior work was the first step in this process and was the first large-scale description of consultation nationally among all Medicare patients. This research proposal represents the next step in this line of investigation. The overall goal of this proposal is to identify drivers to inpatient consultation with a focus on type of physician (e.g., hospitalist, primary care physician) and to quantify the downstream consequences of inpatient consultation. To pursue this goal, we propose two specific aims: (SA1) to identify sources of variation in inpatient consultation by quantifying the effect of hospitalists on the likelihood of inpatient consultation; and (SA2) to examine the impact of consultation on health care resource use following discharge. We will study these questions retrospectively among Medicare beneficiaries with medicine admissions to generalist physicians extracted from Medicare claims over a two-year period. We will employ the necessary hierarchical modeling techniques to address the complex relationships between patients, physicians, hospitals and region of the country and use propensity score analyses to accommodate inherent confounding by indication. Completion of this proposal will result in the first quantification of downstream consequences of specialty use in the hospital and identification of possible areas of under- and overuse of this hospital resource.

Sarinnapha Vasunilashorn, Ph.D.
Beth Israel Deaconess Medical Center
Mentor: Edward R. Marcantonio, M.D., S.M.
"The Psychoneuroimmunology of Postoperative Delirium and its Associated Long-Term Cognitive and Functional Outcomes in Older Adults"

Delirium (an acute change in cognition) is common, morbid, and costly among hospitalized elders, yet our knowledge of its pathophysiology and its associated long-term cognitive and functional outcomes remain limited. Recently, an exciting neuroinflammatory model has emerged that addresses these gaps. In this model, individuals predisposed to a heightened inflammatory response when exposed to an acute stressor, such as surgery or infection, are at increased risk for delirium. These systemic inflammatory mediators may cross the blood brain barrier, result in neuroinflammation, which manifests as delirium, and may in-turn may lead to direct neuronal injury, with resulting long-term cognitive and functional consequences. Two biological mechanisms related to brain distress and neuropsychiatric disorders include the catechol-O-methyltransferase (COMT) gene and S100ß protein (S100ß). COMT, an enzyme that degrades catecholamines (stress hormones), is a key regulator of the stress response and has been associated with cognitive function. Elevated levels of S100ß, a glial-specific marker of neuronal injury, have been related to traumatic brain injury and stroke. Since COMT and S100ß have been linked to several brain disorders, the same mechanisms may be important in delirium. This project will extend and elucidate current work surrounding these biological mechanisms of brain distress and neuropsychiatric disorders, including: the COMT gene and post-translational modification, and S100ß. I will use the Successful AGing after Elective Surgery Study of 566 non-demented adults age =70 who underwent major noncardiac surgery. My Specific Aims: 1) examine the relationship between COMT genotype and methylation,

with postoperative inflammation and incidence of delirium, and 2) investigate the role of neuronal injury as a mediator of postoperative delirium and long-term outcomes. This work will advance the field by enhancing our understanding of the mechanisms of delirium by: elucidating whether genetic regulation of the stress response influences postoperative inflammation and delirium, and determining whether adverse long-term outcomes after delirium are attributed to direct neuronal injury. These findings may be used to identify patients at greatest risk for developing delirium, to assist with delirium monitoring and prognosis, and to develop interventional strategies to reduce the impact of this important geriatric syndrome that threatens independence in older adults.

2014 Grant Recipients

Noah Berman, Ph.D.
Massachusetts General Hospital
Mentor: Sabine Wilhelm, Ph.D.
"Differential Effects of Positive and Negative Mood on OCD Treatment Response"

Obsessive Compulsive Disorder (OCD) is a significantly impairing psychiatric illness that affects 2-3% of the population and is recognized as one of the ten leading causes of disability worldwide. Given the high prevalence, degree of impairment, and substantial financial burden, OCD is recognized as a major public health concern. Research aimed at better treating this debilitating disorder has increased over the past few decades, and exposure with response prevention (EXRP) has emerged as the most effective psychological treatment. However, a sizeable number of patients drop out of, or do not respond to, this intervention. Researchers have posited that the daunting nature of exposure-based therapy is a significant contributor to attrition and that patients' mood state can influence drop out, as well as the perceived acceptability and effectiveness of this intervention. No empirical work, however, has identified how mood affects EXRP. The present study therefore seeks to examine the mechanisms by which mood influences exposure-based treatment. Specifically, I aim to investigate how positive and negative mood states affect the interpretation of OCD-related stimuli and the subjective and physiologic habituation process following exposure.

To examine this research question, I will utilize a well-characterized sample of individuals with OCD. Following diagnostic interviews, participants will be randomly assigned to a sad, neutral (i.e., control), or positive mood induction. To maintain the effects of the mood induction, participants will then be administered an attention-training paradigm. To then assess how participants interpret idiosyncratic OCD-related stimuli, I will utilize self-report scales, pulse oximetry and facial electromyography (fEMG). Lastly, subjective and objective measures of habituation processes will be assessed in the context of a behavioral avoidance test (BAT). This multi-method study will provide pilot data for an NIMH Career Development award proposal, in which I will conduct a more comprehensive examination of how mood affects successful exposure-based therapy by investigating the interaction of psychosocial, neurobiological, and physiological factors. In identifying how mood states impact EXRP, I aim to reduce the substantial public health impact and financial burden of OCD by tailoring interventions to improve the acceptability of exposure-based therapy and account for the affect of comorbid mood disorders.

Kathryn Papp, Ph.D.
Brigham and Women's Hospital

Mentor: Reisa A. Sperling, M.D.
"Using Semantic Memory to Differentiate Normal Aging from Preclinical Alzheimer's Disease"

Background: Alzheimer's disease (AD) and its precursor MCI (Mild Cognitive Impairment) are characterized by frank declines in episodic memory and semantic memory (i.e., memory for meaning, factual knowledge). Recently published guidelines suggest that subtle alterations in cognition may emerge prior to the stage of MCI, in clinically normal (CN) older adults. While episodic memory as it relates to AD-specific biomarkers has been extensively explored in CN older adults, semantic memory has been comparatively understudied. Famous face naming is an ecologically valid and useful semantic memory task that is sensitive to MCI/AD. But no studies, to our knowledge, have explored semantic memory using famous faces in CN adults in relation to AD-specific biomarkers.

Objective: The goal of this project is to determine if decrements in semantic memory are a marker specific to preclinical AD in CN older adults. Doing so may 1) provide a relevant outcome measure to be used in future clinical trials of disease-modifying drugs and 2) provide clinical guidelines for whether declines in semantic memory (the most common cognitive complaint of older patients) is a harbinger of AD.

Methods: We will administer a novel cognitive test of semantic memory entitled the Famous Face Association Test (FFAT) to 100 CN and early MCI older subjects participating in Harvard Aging Brain study. We will assess the relationship between the FFAT and traditional cognitive markers of episodic and semantic memory, amyloid burden, APOE epsilon4 gene status, and structural MRI volumetrics.

Aims and Hypotheses: Our first aim is to identify the psychometric properties of the FFAT and to investigate its relationship to other cognitive markers. We expect the FFAT to be reliable, exhibit good convergent and discriminant validity, and to be associated with episodic memory failure and memory complaints. Our second aim is to determine whether semantic memory decrements are associated with markers of preclinical AD. We expect poorer FFAT performance to be associated with biomarker evidence of increased risk for AD, including greater amyloid burden seen on brain imaging, greater genetic burden (greater number of APOE epsilon4 alleles), and decreased volume in brain areas important for memory (i.e., hippocampus).

2013 Grant Recipients

Jason Andrews, M.D.
Massachusetts General Hospital
Mentor: Edward T. Ryan, M.D., DTM&H
"Evaluating Novel Diagnostic Strategies for Enteric Fever in Rural Nepal"

Every year, 21.6 million people worldwide develop typhoid, with the majority of cases and deaths occurring in South Asia. Serologic diagnostics have limited sensitivity and specificity, while the best available diagnostic--blood culture--is not available in rural, resource-limited settings due to lack of reliable electricity, laboratory infrastructure, and trained laboratory personnel. Working with colleagues at M.I.T., I designed a simple procedure to make culture-based diagnosis feasible without requiring these resources. I led the laboratory development of this procedure and a clinical validation study in urban Nepal that demonstrated excellent concordance with conventional blood cultures. In this research proposal, I detail a series of aims focused on improving diagnosis and treatment of typhoid in resource-limited settings through combining robust clinical prediction rules with this electricity-free culture-based diagnostic. I will do so by 1) applying advanced Bayesian statistical approaches to data generated from a careful study of typhoid among patients presenting with undifferentiated fever; 2) using the electricity-free culture procedure to obtain data on incidence of typhoid and

drug-resistance among febrile patients presenting to rural Nepalese clinical settings; and 3) developing and populating a decision analytic, cost-effectiveness model for diagnosis and treatment of typhoid, using data generated from these clinical studies. Study sites for this research will include Patan Hospital, where we validated the innovative diagnostic, and Bayalpata Hospital, a rural Nepalese hospital where I have worked for the past five years. This research will be mentored by Dr. Edward T. Ryan, an expert in diagnosis of enteric diseases with a focus on South Asia, and Dr. Rochelle P. Walensky, a leader in model-based analysis of cost-effectiveness for infectious diseases diagnostics. This work builds upon my training in epidemiology and modeling and will serve as a foundation for a K01 career development award focused on modeling, operations research and implementation science for enteric diseases diagnostics.

Kimberly Bertrand, Sc.D.
Brigham and Women's Hospital
Mentor: Rulla Tamimi, Sc.D.
"Adolescent Diet, Mammographic Density, and Breast Cancer Risk in Premenopausal Women"

Mammographic density is one of the strongest risk factors for breast cancer and is considered an intermediate marker of risk. We will conduct an epidemiologic investigation to study associations between adolescent diet, mammographic density, and breast cancer risk in premenopausal women. The specific aims of this project are:

1. To test the hypotheses that intakes of total energy, total fat, animal fat, and dairy fat as well as red meat and alcohol during adolescence are positively associated with mammographic density while intakes of carbohydrate, fiber, and vitamin D during adolescence are inversely associated with mammographic density in premenopausal women.

2. To evaluate whether associations observed between adolescent dietary risk factors and premenopausal mammographic density are modified by early life anthropometric characteristics.

3. To test the hypothesis that adjustment for premenopausal breast density accounts, at least in part, for associations between specific adolescent dietary factors and risk of breast cancer.

To address these aims, we will use the unique resources available in the Nurses' Health Study (NHS) II, a long-term follow-up study of premenopausal women. We collected screening mammograms from NHSII participants included in a nested case-control study of breast cancer. Percent breast density was assessed from mammograms using a computer-assisted method. High school dietary data were assessed by a food frequency questionnaire. Data will be available for approximately 967 cases and 1410 controls. We will use multiple linear regression, adjusting for potential confounders, to examine specific adolescent dietary risk factors in relation to average percent breast density among controls. We will also evaluate associations within subgroups defined by early life anthropometric characteristics (e.g., childhood/adolescent somatotype). Finally, we will quantitatively determine whether adolescent diet and premenopausal mammographic density are independently associated with breast cancer risk.

The proposed research will address critical gaps in current knowledge about the nutritional etiology of breast cancer. More importantly, dietary factors during adolescence are potentially modifiable determinants of risk. Identifying such novel risk factors will have a direct impact on prevention messages and future reductions in breast cancer incidence and mortality.

Andrea Enzinger, M.D.
Dana-Farber Cancer Institute

Mentor: Holly Prigerson, Ph.D.
"Characteristics of Effective End-of-Life Communication: Discussing Prognosis and Curability with Advanced Cancer Patients"

For patients with advanced incurable cancer, an accurate understanding of prognosis is fundamental to the ability to accept terminal illness and make appropriate plans at the end-of-life (EOL). Although most patients want accurate prognostic information, a large proportion of advanced cancer patents substantially overestimate their prognosis and inaccurately believe that palliative chemotherapy may cure their disease.

Gaps in communication likely contribute to patients' poor understanding of prognosis, curability and treatment intent, compromising informed decision-making, and contributing to overutilization of aggressive medical care near EOL. Research indicates substantial variability in how oncologists discuss prognosis and EOL medical care. These difficult topics are often discussed selectively, or with vague or euphemistic terminology to soften their emotional impact. Unfortunately, patients could easily misinterpret subtle or ambiguous prognostic messages. Research is needed to understand what communication approaches are most effective at improving patients' understanding of prognosis, curability, and the goals of palliative therapy.

We propose to analyze data from Coping with Cancer 2 (CwC2), an ongoing NCI-funded, multi-site, prospective cohort study, targeting enrollment of 400 patients with advanced metastatic cancer. As part of CwC2, clinic visits after a restaging scan are audiotaped, enabling study of conversations relating to disease progression, prognosis, and EOL planning. Pre- and post-visit surveys assess patients' understanding of curability, prognosis and treatment intent. We will analyze the content of audio-recorded visits (1) to determine the frequency and approach (e.g. direct versus vague) in which prognosis and curability are discussed, and (2) to determine communication elements that favorably impact patients' understanding of prognosis and curability. Secondly, we propose a cross-sectional study of 75 advanced cancer patients, employing semi-structured interviews to explore their perspectives regarding how effectively prognosis, curability, and treatment intent were communicated during their initial oncology consultations. We will probe for specific phraseologies or communication approaches they perceived as particularly informative, or difficult to understand.

Our findings will inform future research in prognostic communication, including the development of a communication training intervention. Moreover, our findings have potential to enhance physicians' communication about prognosis and palliative treatment, improving the informed consent process, and supporting informed decision-making about palliative therapies at EOL.

2012 Grant Recipients

Dae Hyun Kim, M.D., M.P.H.
Beth Israel Deaconess Medical Center
"Comparative Effectiveness of Self-Reported Information, Physical Performance Tests, and Noninvasive Measurements of Vascular Disease Burden in Predicting Persistent Disability in Aging Population"

Over 20% of older Americans report difficulty with at least 1 activity of daily living (ADL) and, in 2004, $135 billion was spent to treat older adults with ADL impairments. Loss of independence (or dependence) in ADLs is an important patient-centered outcome, because it is 'the final common pathway' in aging and the disabling process that results from multiple disease conditions and is a strong predictor of institutionalizations, hospitalizations, and mortality. Therefore, early identification of individuals at risk for ADL dependence is a crucial first step to prevent disability and reduce healthcare costs.

Extensive research has identified a wide range of risk factors and elucidated causal pathways to ADL dependence, but the translation of scientific knowledge into clinical risk prediction has been slow. Our systematic review of the literature found that previous studies of risk factors for disability are limited by: different definitions of ADL disability; failure to consider the severity and duration of disability; lack of information on the optimal combination of previously identified risk factors for prediction; and the absence of comparison among different risk assessment methods, such as self-reported information, physical performance tests, or non-invasive measurements of subclinical disease burden, especially vascular disease.

Leading up to this proposed research, we have recently developed a simple model that uses self-reported information and brief cognitive assessment to predict the 5-year risk of persistent (more than 1 year) dependence with 3 or more ADLs in a large cohort of community-dwelling older adults. Building upon this research, we now propose to: 1) validate our prediction model in an independent dataset, the Cardiovascular Health Study; 2) examine whether our model also predicts other health outcomes, i.e., mortality and hospitalizations; and 3) compare our model with alternative prediction models that use physical performance tests (gait speed, repeated chair stands, and balance) or non-invasive measurements of vascular disease burden (electrocardiography, carotid ultrasound, and ankle-arm index).

In the end, we hope to disseminate a simple assessment tool for persistent ADL dependence and provide comparative evidence on different risk assessment tools. This research will help clinicians objectively assess patients' prognosis and make individualized long-term care plans.

Luke Stoeckel, Ph.D.
Massachusetts General Hospital
"Self-Regulation of Brain Activation in Addiction"

Smoking-related illness causes over 440,000 deaths in the US and over 5 million deaths worldwide annually, and this figure is increasing. Although effective existing therapies double to triple cessation rates, relapse rates remain high. Up to 90% of people who quit smoking relapse within the first year, even with the best treatment available. Thus, we face a critical need to develop a better understanding of the neurobiological underpinnings of addictive processes, and of relapse in particular, in order to develop targeted relapse prevention therapies that help people to maintain abstinence. Most relapse occurs following smoking cue exposure. Tools now exist to evaluate individual patterns of abnormal cortical and subcortical brain reactivity to smoking cues in relapse prone smokers and to train people to modulate this abnormal smoking-related cue-associated brain reactivity with the aim of ameliorating disease-associated craving and compulsive urges. This revised project will test such a tool, real-time functional magnetic resonance imaging (fMRI) neurofeedback used with emotion regulation strategies, as a novel approach to understanding and potentially modulating the neurobiology of addiction. This study is made possible by an ongoing collaboration between our research team at the Massachusetts General Hospital (MGH) Center for Addiction Medicine, who have a track record of study of novel treatments for nicotine dependence, and Drs. John Gabrieli, Susan Whitfield-Gabrieli, and Ann Graybiel, a highly innovative and productive team of cognitive neuroscientists at the Massachusetts Institute of Technology (MIT), who have pioneered this novel imaging technique. The proposed work has the potential to produce improved understanding of brain mechanisms underlying relapse and potentially, a novel therapy that could reduce the enormous morbidity and mortality caused by chronic, relapsing addiction to smoked tobacco, and also offers the potential for improved understanding and treatment of related disorders such as gambling and certain phenotypes of obesity that involve compulsive urges and failure of inhibitory control.

2011 Grant Recipients

David Chan, M.D., M.Sc.
Brigham and Women's Hospital
"Social Networks and Peer Effects among Emergency Department Physicians"

The notion that physicians can be socially incentivized by the presence of their peers is intuitive. However, to my knowledge, the nature of these "peer effects" among physicians has not previously been studied. My long-term objective is to study the effect of social networks on the behavior of individual physicians and on the overall productivity of health care organizations.

Specifically, I will evaluate the effects of emergency department physicians on each other as they work together. My specific aims are threefold. First, I will measure peer effects on individual productivity -- along dimensions of speed of care, quality of care, and teaching. I predict tradeoffs between more observable dimensions (e.g., speed of care) and less observable ones (e.g., quality of care), and I expect that peer effects will be stronger among more socially connected peers. Second, I will study peer effects on the choice of patients by physicians. Individual physicians may want to choose easy patients (i.e., "cherry pick"), but social networks may mitigate this by social pressure and appropriate coordination of work. Third, I will study the effect on overall emergency department productivity under a new system that disallows physicians from choosing their own patients.

Two complementary features of my research design will allow us to accomplish my aims. First, I have detailed, longitudinal data on individual physicians and the patients that they see, involving sufficient variation in the teams of physicians working with each other. Second, my emergency department is undertaking a natural experiment in March of 2011 in which the rules of patient assignment will disallow physicians from choosing their own patients.

My research will shed light on how health care organizations should design their social networks implicit in team structures and the rules that govern behavior within teams. Specific implications include how organizations should match peers with each other, how transparent they should make productivity measures among peers at the expense of less transparent measures, and how much they should constrain implicitly social behaviors such as the choice of patients among physicians.

Peter Smulowitz, M.D., M.P.H.
Beth Israel Deaconess Medical Center
"Massachusetts Health Reform and Emergency Department Utilization by Underserved Populations"

With the passage of the Patient Protection and Affordable Care Act (ACA) of 2010, the landscape of the US health system will change markedly. Similar to the ACA, the Massachusetts health reform legislation enacted in 2006 was designed to reduce the number of Massachusetts residents without health insurance.

One of the principal expected benefits of the Massachusetts legislation was that it would result in decreased utilization of Emergency Departments (EDs). However, ED use may be impacted by many factors aside from insurance status. The ED is used disproportionately by underserved populations without access to adequate primary care, many of whom are members of racial and ethnic minorities who lack insurance or are insured by the Medicaid program.

The proposed study will take advantage of comprehensive statewide data on ED utilization available in Massachusetts to study the impact of MA health reform on use of the ED. Thus, the results of this study will be an important guide to policy makers about the potential impact of health reform on ED utilization as the ACA is implemented across the nation.

Using data from the Massachusetts Division of Health Care Finance and Policy Acute Hospital Case Mix Databases from the years 2005 through 2010, we will examine the following specific aims:

Aim 1: To determine the impact of Massachusetts health care reform on ED utilization for low severity and ambulatory care sensitive visits using geographic variation (at the zip code level) in the percentage insured as our method of identification of changes resulting from health reform.

Aim 2: To estimate the effect of health reform on ED utilization by underserved populations -- defined by race and zip-code derived measures of socioeconomic status and social disorganization.

In order to accomplish these aims, we will utilize a validated algorithm to measure ED visit severity and a difference-in-differences analytic framework that will allow us to make causal inferences.

2010 Grant Recipients

Yee-Ming Chan, M.D., Ph.D.
Massachusetts General Hospital
"Using Kisspeptin to Interrogate the Human GnRH Neuron in vivo"

The neuropeptide kisspeptin has recently been found to be a critical reproductive hormone. Kisspeptin activates the reproductive endocrine cascade by stimulating neurons in the hypothalamus to release gonadotropin-releasing hormone (GnRH), which stimulates the pituitary gland to secrete luteinizing hormone (LH) and follicle-stimulating hormone (FSH), which in turn stimulate the gonads to produce gametes and sex steroids (testosterone in men, estrogen in women). Kisspeptin is essential for human reproductive function, as mutations that disrupt the kisspeptin receptor cause idiopathic hypogonadotropic hypogonadism (IHH), a condition characterized by a failure to undergo normal puberty and consequent infertility.

Several groups (including ours) have identified a number of genetic mutations that underlie IHH. These studies have shown that IHH can result from the absence of GnRH neurons, or from a lack of upstream signals (such as kisspeptin) that are essential for normal GnRH secretion. However, for the ~75% of IHH patients who do not carry an identifiable mutation, it is not possible to determine which of these is the underlying mechanism; to date, there has been no method to probe the function of GnRH neurons in vivo. Because kisspeptin directly stimulates the GnRH neuron, exogenous administration of kisspeptin can now be used to assess GnRH neuronal function.

This project is a phase I/II clinical trial involving the administration of kisspeptin to human subjects, both healthy volunteers and individuals with IHH. Kisspeptin administration to healthy volunteers will reveal the precise effects of kisspeptin on GnRH secretion and will establish normal ranges for kisspeptin responses. Kisspeptin administration to IHH patients will be used to determine which of these patients retain functional GnRH neurons, a finding that may have prognostic implications.

These studies will allow us to characterize the pathophysiology of IHH and may also lead to the use of kisspeptin as diagnostic tool for other reproductive disorders, such as delayed puberty in adolescents. Furthermore, these studies are the first steps towards developing kisspeptin as a clinical treatment to stimulate or suppress the reproductive endocrine axis, with potential applications in the treatment of infertility, precocious puberty, and hormone-sensitive tumors such as breast cancer and prostate cancer.

Natalie Shaw, M.D.
Massachusetts General Hospital
"Effect of Sleep Apnea on Nocturnal GnRH/LH Secretion in Children in Early Puberty"

The earliest physiological sign of puberty in both boys and girls is an augmentation of the pulsatile secretion of hypothalamic gonadotropin-releasing hormone (GnRH) and pituitary luteinizing hormone (LH). This augmentation initially occurs only during sleep. We hypothesize that the hypoxic episodes and arousals which disrupt sleep in children with obstructive sleep apnea (OSA) will disrupt the nocturnal GnRH/LH secretory pattern of children with OSA in the early stages of puberty. Specifically, we expect children with OSA in early puberty to have decreased LH pulse frequency and amplitude proportional to the severity of their sleep apnea.

To investigate this hypothesis, we will enroll 15 children in early puberty with OSA treated with a continuous positive airway pressure (CPAP) machine. Each child will undergo two studies consisting of a polysomnographic sleep study with simultaneous frequent blood sampling to detect LH pulses with or without CPAP in random order, such that each child serves as his own control, to determine whether LH pulse frequency and amplitude are decreased in the absence of CPAP. We will then investigate whether EEG arousals in the absence of hypoxia can produce a decrement in LH pulse frequency and amplitude. We will enroll another 15 children, and each child will undergo two polysomnographic sleep studies with frequent blood sampling. CPAP will be used in both studies during one of which auditory stimuli will be used to induce EEG arousals. The order of the studies will be randomized. These protocols will also allow us to analyze the connection between sleep stage and GnRH/LH pulses during puberty.

Given the high prevalence of OSA in children (1-4%), there is a potentially large population of children at risk for reproductive dysfunction in the form of failure to progress or delayed progression through puberty. These studies will allow us to define this risk as well as to provide greater insights into the basic physiology which ties GnRH/LH pulses to sleep.

2009 Grant Recipients

Stacey Kenfield, Sc.D., M.Sc.
Harvard School of Public Health
"Diet, Lifestyle, Biomarkers, and Prostate Cancer Survivorship"

Over 2 million men in the United States are prostate cancer (PCa) survivors. Many studies have examined dietary and lifestyle factors in relation to PCa incidence, but few have assessed their impact on PCa progression and survival. PCa has a very heterogenous course; in some men, the disease rapidly progresses to metastases and death despite aggressive therapy, but in many, the course is indolent even with no treatment at all. Intriguing evidence suggests that diet and lifestyle after PCa diagnosis can affect prognosis. To address this important gap, I propose to evaluate three promising factors: fish intake, statin use, and physical activity and integrate these exposure data with biomarker data to explore relevant biologic pathways. These factors have been related to risk of advanced PCa, and have anti-angiogenic, anti-inflammatory, anti-proliferative, and pro-apoptotic effects, which may delay disease progression and improve survival. The specific aims are to examine the relation of PCa recurrence and mortality with: 1) high fish intake (both before and after diagnosis); 2) fish intake and markers of angiogenesis in the tumor tissue; 3) statin use and markers of angiogenesis, apoptosis, proliferation, and inflammation in the tumor tissue; and 4) high levels of physical activity (both before and after diagnosis). I will use data from approximately 3,500 participants in the Health Professionals Follow-up Study (HPFS) diagnosed with PCa who are followed every 2 years since diagnosis for recurrence outcomes. The HPFS is an ongoing prospective cohort study of 51,529 men that began in 1986, and dietary and other covariate data are collected

every two to four years. Cox proportional hazards regression will be used to analyze the associations between diet and lifestyle factors and time to PCa recurrence and PCa-specific death. The findings from this research will be useful in determining whether these three promising factors may be beneficial for the growing population of men diagnosed with PCa; the biomarker analyses will determine potential mechanisms for those effects.

Angela Leung, M.D.
Boston University Medical Center
"Breast Milk Iodine and Perchlorate Concentrations: Effect on Infant Thyroid Function"

Context: Breastfed infants are reliant on maternal iodine for the production of thyroid hormones required for normal neurodevelopment. Recent studies have demonstrated a decrease in the dietary iodine intake of U.S. women of childbearing age. Environmental exposure to perchlorate, a competitive inhibitor of the sodium/iodide symporter (NIS), is ubiquitous in the U.S. Perchlorate exposure could potentially decrease NIS-mediated uptake of iodine into breast milk and infants' thyroid and could directly affect infant thyroid function. Thiocyanate, a byproduct of cigarette smoke and another inhibitor of NIS, may also decrease breast and thyroidal iodine utilization.

Objective: To cross-sectionally examine the relationships between iodine sufficiency of lactating women and their 1-2 month old infants, environmental perchlorate and cigarette smoke exposure, and infant thyroid function.

Participants: 275 healthy 1-2 month old breastfed infants and their lactating mothers in the Boston area.

Measurements: Concentrations of infant urinary iodine and perchlorate; infant serum TSH and free T4; maternal urinary iodine, perchlorate, and thiocyanate (as a marker for cigarette smoke exposure); and breast milk iodine, perchlorate, and thiocyanate.

Significance: The present proposal will be the first study to specifically examine relationships between iodine concentrations, perchlorate and cigarette smoking exposures, and thyroid function in breastfed infants. These data, far larger than any previous U.S. survey, will help to define adequate dietary iodine intake for breastfed infants and their mothers, and will also determine whether environmental perchlorate and cigarette smoking exposure have deleterious effects on infants' thyroid function.

2008 Grant Recipients

Kimmie Ng, M.D., M.P.H.
Dana-Farber Cancer Institute
"Influence of the vitamin D pathway on survival in patients with colorectal cancer"

Nutritional therapies are the most common form of complementary therapy among cancer patients. A consensus panel of the American Cancer Society recommended, "Properly conducted studies of the effect of nutrition and physical activity on the prognosis of cancer survivors are urgently needed, and should be a high priority for all academic and research funding agencies." A growing body of evidence suggests that vitamin D inhibits growth of colorectal cancer cells and may improve the survival of patients with colorectal cancer. Using data from two large ongoing cohort studies, the Nurses' Health Study and the Health Professionals Follow-Up Study (160,000 participants), as well as a large, completed National Cancer Institute sponsored chemotherapy clinical trial in stage III colon cancer, we will examine the influence of various aspects of the vitamin D pathway on colorectal cancer patient outcomes. We will evaluate the relationship between plasma levels of 25 –

hydroxyvitamin D [25(OH)D], the main form of vitamin D in the blood, and survival in colorectal cancer patients, as well as the association between a predicted vitamin D score calculated from the main determinants of vitamin D status and patient survival. Moreover, we propose to investigate the impact of genetic variations in an important protein in the vitamin D pathway, the vitamin D receptor, as well as expression of the protein, on patient survival. Finally, interactions between patient blood levels of vitamin D and molecular factors within the tumors, such as K – ras mutations, will be explored. With the advantages of prospective longitudinal assessment of nutritional and lifestyle factors, paraffin – embedded tumor specimens to examine how vitamin D interacts with molecular alterations in tumors, prospectively collected blood and germline DNA specimens, and comprehensive data on cancer recurrence and mortality provided by these cohorts, we hope to further elucidate the role of the vitamin D pathway in colorectal cancer. Our results could potentially lead to a better understanding of the underlying biology of colorectal cancer, and to the identification of novel targets for therapeutic intervention.

Joshua Roffman, M.D.
Massachusetts General Hospital
"Altered one-carbon metabolism in schizophrenia: molecular and neuroimaging correlates of folate response"

Schizophrenia is a devastating neuropsychiatric disorder affecting 1% of the population. Although certain schizophrenia symptoms can be managed with antipsychotic medications, there remain no good treatment options for the most debilitating aspects of the disorder-cognitive impairment and negative symptoms. These symptoms substantially disrupt social and occupational function, and inflict a terrible burden on affected patients, their family members, and society at large.

Up to 80% of an individual's risk for schizophrenia relates to genetic factors, although the effects of individual genes have been difficult to measure. We are using a variety of new, cross-disciplinary tools to magnify the signals of risk genes, by examining their effects on the levels of molecules, cells, and regional brain function in schizophrenia patients. Our work has focused on a promising candidate gene, MTHFR, that plays an important role in how the body processes folate. Folate is a B vitamin that comes from dietary sources, and deficiencies in folate have been tied to a variety of neuropsychiatric illnesses including schizophrenia. The MTHFR gene breaks down dietary folate into methyl groups, which influence the activity of genes that regulate brain chemistry. We are particularly interested in how the MTHFR gene influences the expression of a protein called COMT, which affects dopamine signaling in a part of the brain that has been consistently implicated in schizophrenia, the dorsolateral prefrontal cortex (DLPFC).

We have shown that a common genetic variant in MTHFR increases the severity of negative symptoms and cognitive impairment in the disorder, and that these effects are worsened in patients with low folate intake. Using functional MRI scans, we have seen that the MTHFR gene also affects activity in the DLPFC during memory tasks in schizophrenia patients. The proposed research will determine whether MTHFR's effect on methyl groups and COMT expression drive its subsequent effects on DLPFC activity and cognitive impairment in schizophrenia. We will also determine whether treatment with folic acid helps to reverse the effects of MTHFR on COMT and DLPFC activity. These studies may provide vital insights into the genetic basis of schizophrenia, and will apply these insights directly to a promising new treatment for cognitive impairment.

2007 Grant Recipients

Mary Keebler, M.D.

Massachusetts General Hospital
"Identification of Common DNA Sequence Variants Related to Blood Lipid Traits"

Jaime Murphy, M.D.
Boston University Medical Center
"Circulating Mesenchymal Precursors with Fibrogenic Potential in Asthma"

2006 Grant Recipients

Serena Mascieri, M.D.
Dana-Farber Cancer Institute
Prevalence of Germline E-Cadherin Mutations in Women with Lobular Breast Cancer

Maitreyi Mazumdar, M.D., M.P.H.
Children's Hospital Boston
"Health Insurance and Utilization of Services by Children with Epilepsy"

2005 Grant Recipients

Robert Ajemian, Ph.D.
Massachusetts Institute of Technology
"Dynamic Motor Learning in Alzheimer's Disease"

Jinbo Fan, Ph.D.
Massachusetts Institute of Technology
"Linkage Disequilibrium Mapping on Candidate Genes Across Chromosome 6q16-22 Bipolar Disorder Locus"

2004 Grant Recipients

Tina Huang, Ph.D.
Tufts University School of Medicine
"The Relationship of Fish and Essential Fatty Acids to Dementia and Alzheimer's Disease"

Sigall Kassutto, M.D.
Massachusetts General Hospital
"Predictors of Time to Virologic Supression and Disease Progression after Initiation of Antiretroviral Therapy in Acute HIV-1 Infection"

Juliette C. Madan, M.D.
New England Medical Center
"Indomethacin Use for Closure of Patent Ductus Arteriosus in VLBW Infants: Association with Necrotizing Enterocolitis and Spontaneous Intestinal Perforation"

2003 Grant Recipients

Heike A. Bischoff, M.D., M.P.H.
Brigham and Women's Hospital
"Effects of Vitamin D&K on symptomatic Osteoarthritis of the Hip and Knee"

Richard E. Frye, M.D., Ph.D.
Children's Hospital Boston
"Developmental phonological dyslexia: Neural mechanisms"