

# **Charles A. King Trust Postdoctoral Fellowship Program**

*Clinical and Health Services Research*

## **2011 Grant Recipients**

### **David Chan, M.D., M.Sc. (Clinical and Health Services Research)**

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. (Clinical and Health Services Research)**

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. (Clinical and Health Services Research)**

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. (Clinical and Health Services Research)**

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. (Clinical and Health Services Research)**

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 heterogeneous 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. (Clinical and Health Services Research)**

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. (Clinical and Health Services Research)**

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. (Clinical and Health Services Research)**

*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. (Clinical and Health Services Research)**

*Massachusetts General Hospital*

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

### **Jaime Murphy, M.D. (Clinical and Health Services Research)**

*Boston University Medical Center*

"Circulating Mesenchymal Precursors with Fibrogenic Potential in Asthma"

## **2006 Grant Recipients**

### **Serena Mascieri, M.D. (Clinical and Health Services Research)**

*Dana-Farber Cancer Institute*

Prevalence of Germline E-Cadherin Mutations in Women with Lobular Breast Cancer

### **Maitreyi Mazumdar, M.D., M.P.H. (Clinical and Health Services Research)**

*Children's Hospital Boston*

"Health Insurance and Utilization of Services by Children with Epilepsy"

## **2005 Grant Recipients**

### **Robert Ajemian, Ph.D. (Clinical and Health Services Research)**

*Massachusetts Institute of Technology*

"Dynamic Motor Learning in Alzheimer's Disease"

### **Jinbo Fan, Ph.D. (Clinical and Health Services Research)**

*Massachusetts Institute of Technology*

"Linkage Disequilibrium Mapping on Candidate Genes Across Chromosome 6q16-22 Bipolar Disorder Locus"

## **2004 Grant Recipients**

### **Tina Huang, Ph.D. (Clinical and Health Services Research)**

*Tufts University School of Medicine*

"The Relationship of Fish and Essential Fatty Acids to Dementia and Alzheimer's Disease"

### **Sigall Kassutto, M.D. (Clinical and Health Services Research)**

*Massachusetts General Hospital*

"Predictors of Time to Virologic Suppression and Disease Progression after Initiation of Antiretroviral Therapy in Acute HIV-1 Infection"

### **Juliette C. Madan, M.D. (Clinical and Health Services Research)**

*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. (Clinical and Health Services Research)**

*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. (Clinical and Health Services Research)**

*Children's Hospital Boston*

"Developmental phonological dyslexia: Neural mechanisms"