HARVARD CATALYST

THE HARVARD CLINICAL AND TRANSLATIONAL SCIENCE CENTER

Biomedical Collaborative Pilot Grants
Cycle 2

The Harvard Catalyst Pilot Grants Program sponsored three cycles of Biomedical Collaborative Pilot Grants, which were directed at improving human health. These grants aimed to support clinical or translational research pilot studies that would lead to sustainable, innovative and collaborative projects with a high potential to impact human health.

The Cycle 2 funding opportunity was open to any faculty member holding a Harvard University faculty appointment. A collaborative team was required and inter-disciplinary and inter-institutional collaborations were encouraged. In this cycle, 65 grants were awarded of up to $50,000 per funded proposal to support a one-year pilot research project.

Funding decisions for the second cycle of Biomedical Collaborative Pilot Grants were announced in October 2009.

For more information about these awards, see the following news article.

Targets of Epigenetic Dysregulation in Hematologic Malignancies

Principal Investigator: Suneet Agarwal, MD, PhD, Children's Hospital Boston

Co-Investigator(s): Scott Armstrong, MD, PhD, Children's Hospital Boston
George Daley, MD, PhD, Children's Hospital Boston
Anjana Rao, PhD, Immune Disease Institute

The molecular characterization of genetic alterations in leukemias and myeloproliferative neoplasms has been critical in terms of illuminating disease mechanisms and providing therapeutic targets. Epigenetic changes, including cytosine methylation of DNA, are increasingly recognized as contributing to the pathogenesis of cancer, but elucidating the mechanisms and targets of epigenetic dysregulation remains an important challenge. Recently, members of the TET gene family have been shown to be frequent targets of genetic disruption in a wide spectrum of adult and pediatric hematologic neoplasms. Independently, biochemical studies have shown that TET proteins catalyze the conversion of methylcytosine (mC) in mammalian DNA to a novel base, 5-hydroxymethylcytosine (hmC). Here we hypothesize that TET proteins play a key role in altering the DNA methylation status of critical genetic loci during normal hematopoiesis, and that disruption of this process leads to malignant transformation. We propose to develop and apply novel technologies aimed at the sensitive and specific detection of mC and hmC in genomic DNA. We will use candidate-locus and genome-wide approaches to profile TET-mediated modification of mC and hmC during normal and malignant hematopoiesis. In subsequent work we will use these techniques to validate in patient samples the contribution of epigenetically dysregulated candidate genes to the pathogenesis of TET-dependent leukemias. Our proposed studies will bring together Harvard investigators with expertise in the biochemistry of TET proteins, epigenetics, and stem cell development, establishing new collaborations for the ongoing study of epigenetic changes in normal and malignant stem cell development and providing novel targets for therapy.

Inhibitors of the Deoxygenation-activated Cation Conductance in Sickle Erythrocytes: A New Adjunct Therapeutic Target in Sickle Disease

Principal Investigator: Seth Alper, MD, PhD, Beth Israel Deaconess Medical Center

Co-Investigator(s): Carlo Brugnara, MD, Children's Hospital Boston

We have developed an alternate adjunct therapeutic approach to the treatment of sickle disease by decreasing the intra-erythroid concentration of Hemoglobin S (HbS) to prolong the "delay time", the period between deoxygenation and rapid polymerization of deoxyHbS. We do so by swelling erythrocytes via blockade of potassium and chloride leaks. We identified clotrimazole as a blocker of the erythroid Ca-gated K channel KCa3.1/IK1, also known as the "Gardos channel". This discovery led to development and successful Phase III clinical testing in sickle patients of the proprietary Gardos channel blocker, senicapoc. Gardos channel activation requires elevation of cytosolic free Ca2+, a process triggered by deoxygenation only in HbSS erythrocytes. We have shown that deoxygenation-induced elevation of cytosolic free Ca2+ in sickle cells is paralleled by activation of Ca-permeable cation channel activity. Channel activity is reversible upon reoxygenation, and is inhibited by carbon monoxide, an inhibitor of HbS polymerization. We hypothesize that a small molecule blocker of the deoxygenation-activated cation channel will synergize with senicapoc to prevent shrinkage of deoxygenated sickle erythrocytes, prolong the delay time for HbS polymerization, and so synergize with hydroyxurea in the treatment of sickle disease. Initial pharmacological characterization of this deoxygenation-activated Ca-permeable cation channel of sickle erythrocytes has revealed several nonspecific inhibitors. We therefore propose to perform a high-throughput screen to discover novel small molecule inhibitors of the deoxygenation-induced elevation of cytosolic free Ca2+ in sickle erythrocytes. These will serve as lead compounds for new drug treatments of sickle disease.

A Potential Novel Pathway of Pathological Vascularization of the Retina

Principal Investigator: Zolt Arany, MD, PhD, Beth Israel Deaconess Medical Center

Co-Investigator(s): Magali Saint-Geniez, PhD, Schepens Eye Research Institute

Retinopathy of prematurity (ROP) and other neovascular diseases of the eye, like diabetic retinopathy and “wet” age-related macular degeneration, are major causes of blindness world-wide. ROP is the leading cause of blindness in premature and very-low-birth-weight infants. Standard of care for ROP reduces blindness by only 25%, and is destructive to the retina, calling for a deeper understanding of mechanisms leading to ROP and other neovascular diseases of the eye. We have recently uncovered a novel and powerful angiogenic pathway, involving the transcriptional coactivator PGC-1alpha, a potent regulator of metabolism in many tissues. We hypothesize here that this pathway also operates in retinas, and that PGC-1alpha contributes to abnormal neovascular outgrowth in ROP. Our preliminary data support this hypothesis. We propose to: (1) determine the role of PGC-1alpha during normal retinal development; (2) test if and how PGC-1alpha regulates VEGF and other angiogenic factors in various retinal cell types; and (3) determine the role of PGC-1alpha in pathologic retinal neovascularization. Mice genetically modified to lack PGC-1alpha will be used, as well as an established murine model of ROP. We are both young investigators, one with expertise in transcriptional regulation and metabolism (ZA), the other with expertise in angiogenesis and retinal pathology (MS). We will also have consultative support from Dr. Pat D’Amore, a world expert in retinal diseases. We are therefore ideally poised to perform these exciting experiments. The experiments will likely open new research avenues, and may lead to new approaches to treating ROP and other neovascular retinal diseases.

Development of Dendritic Cell and T Cell Therapy for PML

Principal Investigator: David Avigan, MD, Beth Israel Deaconess Medical Center

Co-Investigator(s): Igor Koralnik, MD, Beth Israel Deaconess Medical Center
Jacalyn Rosenblatt, MD, Beth Israel Deaconess Medical Center
Dimitrios Tzachanis, MD, PhD, Beth Israel Deaconess Medical Center

Progressive Multifocal Leukoencephalopathy (PML) is a deadly opportunistic infection of the brain caused by the polyomavirus JC (JCV). It is found in patients with HIV disease, following solid organ and bone marrow transplantation and in patients undergoing immunosuppressive therapy for malignancy and autoimmune disorders. While there is currently no therapy for PML, cellular immunity against JCV has been associated with a favorable outcome. The development of strategies to enhance JCV-specific cellular immune response in PML patients is urgently needed. Dendritic cells (DC) are potent antigen presenting cells that are crucial for the induction of primary viral immunity and the expansion of viral specific T cells with an activated phenotype. We have demonstrated that DC pulsed with JC virus peptides can effectively enhance the cellular immune response against JCV *in vitro*. However, active vaccination strategies may be limited by lymphopenia and effector cell dysfunction in PML patients. Adoptive immunotherapy with *ex-vivo* expanded T cells may be more effective at generating effective anti-viral immune responses. In pre-clinical tumor model, we have demonstrated that ligation of the costimulatory complex and blockade of the PD-1 inhibitory pathway augments response to DC based vaccination. In this proposal, we will examine the phenotypic and functional characteristics of T cells undergoing sequential stimulation with DCs pulsed with JC viral antigens and anti-CD3CD28 in the presence or absence of anti-PD-1 antibody. Based on preclinical findings, a clinical trial in which patients with PML are treated with pulsed DC alone or in combination with educated T cells is planned.

A Novel Diagnostic Test for Tuberculosis Utilizing Antibodies Specific For Siderocalin-Carboxymycobactin Complexes

Principal Investigator: Meghan Baker, MD, Massachusetts General Hospital

Co-Investigator(s): Bobby J. Cherayil, MD, Massachusetts General Hospital
D. Branch Moody, MD, Brigham and Women's Hospital
Megan B. Murray, MD, Harvard School of Public Health

One-third of the world's population is estimated to be infected with *Mycobacterium tuberculosis* (MTB), 9 million people develop the disease each year, and almost 2 million die annually from the disease. There is an urgent need for rapid diagnostic methods to identify patients with tuberculosis. The ideal test would be a point-of-care urine dipstick that would identify individuals with MTB, especially those co-infected with HIV in whom conventional testing has a low yield. We propose a novel diagnostic approach based on the detection of carboxymycobactin, a secreted MTB siderophore, complexed to the soluble mammalian protein siderocalin. Siderocalin, which is secreted in response to bacterial infection, binds carboxymycobactin with high affinity. This complex is freely filtered in the urine. We propose to generate a complex of purified MTB carboxymycobactin bound to a recombinant glutathione S-transferase-siderocalin fusion protein. Mice immunized with the complex will be used to create B cell hybridomas, which will then be screened for monoclonal antibodies specific for the siderocalin-carboxymycobactin complex as opposed to siderocalin alone. Such antibodies will be tested in an ELISA to determine if they are able to detect carboxymycobactin bound to siderocalin in tissue culture models of MTB infected cells. In future studies, we will examine the ability of this assay to distinguish individuals with MTB infection from those who are healthy or are infected with other bacteria. A urine ELISA that could identify a patient with smear negative tuberculosis could be used in resource limited settings and would improve individual outcomes and decrease transmission.

Understanding and Overcoming Barriers to Linkage to HIV Care in Durban, South Africa

Principal Investigator: Ingrid Bassett, MD, MPH, Massachusetts General Hospital

Co-Investigator(s): Laura Bogart, PhD, Children's Hospital Boston
Jeffrey Katz, MD, MS, Brigham and Women's Hospital
Elena Losina, PhD, Brigham and Women's Hospital
Rochelle Walensky, MD, MPH, Massachusetts General Hospital

Over 5 million people are living with HIV in South Africa; an estimated 300,000 South Africans per year die of the disease. Despite the increasing availability of antiretroviral therapy (ART), only a fraction of those newly diagnosed with HIV successfully link to HIV care and initiate treatment. The period following a new diagnosis, but prior to starting ART, is a time of high, but potentially preventable, mortality. Yet, few studies have examined patient or contextual reasons or remedies for failure to link to care in South Africa. Building on a productive collaboration between US and South African investigators, we propose the following specific aims: 1) To perform in-depth interviews and focus groups among HIV-infected people to identify barriers to successful entry into HIV care; and, 2) To perform a randomized, controlled pilot study of a short messaging service (SMS) mobile phone reminder intervention to improve linkage to care for newly diagnosed HIV-infected outpatients in Durban, South Africa. Through a new research partnership with a behavioral scientist and a transition from our longitudinal cohort study design to an intervention trial, our multi-disciplinary team is uniquely poised to examine clinical, structural, and psychosocial reasons for failure to initiate ART, and to evaluate the feasibility and efficacy of an intervention to improve entry into care. This work will provide preliminary data for an NIH R01 application for a large, randomized trial of a multi-faceted intervention to improve linkage to HIV care for South Africans during the critical period following a new HIV diagnosis.

Search for a Metazoan Phosphate Sensor

Principal Investigator: Clemens Bergwitz, MD, Massachusetts General Hospital

Co-Investigator(s): Norbert Perrimon, PhD, Harvard Medical School

Phosphate homeostasis is crucial in health and disease. Hypophosphatemia leads to rickets or osteomalacia, while hyperphosphatemia causes vascular and tissue calcifications and is associated with mortality in chronic kidney disease. The endocrine regulation of human phosphate homeostasis involves parathyroid hormone (PTH), 1,25-dihydroxy-vitamin D (1,25(OH)2D) and the novel hormonal regulator fibroblast growth factor 23 (FGF23), however it is to date completely unknown, how mammalian cells sense phosphate. We have shown that exposure of the mouse bone marrow stromal cell line ST-2 to 10 mM sodium-phosphate stimulates phosphorylation and thus activation of p42/p44 MAPK (ERK1/2). ERK1/2 activation by phosphate likely involves cellular uptake of phosphate and activation of novel intracellular signaling molecules. Just like in ST-2 cells phosphate induces ERK-phosphorylation in Drosophila S2R+ cells. Therefore, we propose to perform a genome-wide RNAi screen in Drosophila cells for phosphate-induced ERK-phosphorylation using an established robust protocol. Identified hits will then be validated by RNAi in mammalian ST-2 cells and may lead to novel insights for human disorders of phosphate homeostasis.

Point-of-purchase Interventions to Reduce Sugar-sweetened Soft Drink Consumptions in College Cafeterias

Principal Investigator: Jason Block, MD, MPH, Harvard Pilgrim Health Care/DPM

Co-Investigator(s): Amitabh Chandra, PhD, The John F. Kennedy School of Government at Harvard University
Matthew Gillman, MD, SM, Harvard Pilgrim Health Care/DPM
Ken Kleinman, ScD, Harvard Pilgrim Health Care/DPM

The transition to college appears to be an especially challenging period for weight maintenance among young adults. Blunting the Freshman 15 and any additional weight gain during the college years could be an important tool in the fight against the obesity epidemic in the U.S. One major source of calories for young adults is sugary soft drinks, contributing 230 calories per day to their daily caloric intake. Intervening through education and price mechanisms at the point-of-purchase potentially could decrease consumption and, therefore, reduce weight gain. A prior project in a hospital cafeteria demonstrated that a 35% price increase on sugary soft drinks was successful in reducing consumption of these beverages while a flyer-based education campaign was not. We propose a multi-site intervention in 8 colleges, including 2 historically-black colleges, to test interventions intended to decrease consumption of sugary soft drinks -- a price increase, a flyer-based educational campaign discouraging consumption, and an alteration of the default presentation of these beverages. We also will survey a random sample of students in each college before and after the intervention to assess whether knowledge and behaviors changed as a result. The catalyst grant would provide funding for focus groups in 6 of the 8 colleges to further refine the planned intervention.

Can a Dynamic Attention Test Effectively Predict Medically At-risk Older Drivers?

Principal Investigator: Alexandra Bowers, PhD, Schepens Eye Research Institute
Todd Horowitz, PhD, Brigham and Women's Hospital

Co-Investigator(s): Matthew Bronstad, PhD, Schepens Eye Research Institute
Lissa Kapust, MSW, Beth Israel Deaconess Medical Center
Margaret O'Connor, PhD, Beth Israel Deaconess Medical Center

Our aim is to evaluate whether a computerized dynamic visual attention test is predictive of driving performance in elderly and cognitively-impaired populations. Effective prediction of which older persons are safe to drive is a major public health challenge. Age-related impairments in cognition and/or visual function may affect deployment of visual attention, an important component of safe driving. In particular, driving involves interacting with a moving, changing world, requiring constant updating of cognitive representations. The existing Useful Field of View and Trail-Making tests, commonly used to evaluate visual attention when predicting at-risk drivers, do not have a dynamic component. We believe that this may account for why the majority of variance in driving performance is still unexplained. We propose to investigate whether a multiple object tracking (MOT) task is predictive of driving performance. MOT simultaneously measures sustained, selective, and divided attention, in a dynamic situation. We will test elderly participants with and without cognitive impairments on a set of MOT-based tasks as well as other 'static' attention tests, and will use these measures to predict performance in an on-road test. We believe that MOT may provide a simple and cost-effective test for identifying at-risk older drivers. This project will foster new collaborations between basic researchers, clinical researchers and driving rehabilitation specialists to provide preliminary data for studies which could substantially improve public health by identifying individuals at risk for motor vehicle accidents.

Elucidating the Role of Soluble Guanylate Cyclase α1 in the Pathogenesis of Elevated IOP and Glaucoma Using a Novel Murine Model

Principal Investigator: Emmanuel Buys, PhD, Massachusetts General Hospital

Co-Investigator(s): Bruce Ksander, PhD, Schepens Eye Research Institute

Glaucoma is an increasingly prevalent disease that results in vision loss through the death of retinal ganglion cells. Although mutations in several genes have been implicated in the development of glaucoma, the exact molecular mechanisms that trigger death of retinal ganglion cells and loss of vision are poorly understood. Our preliminary data, obtained in a collaboration between Dr. Buys (MGH) and Dr. Ksander (Schepens Eye Research Institute), show that mice deficient in the α1 subunit of soluble guanylate cyclase (sGCα 1-/- mice) spontaneously develop blockage of the outflow pathway of aqueous humor and high intraocular pressure (IOP), suggesting a central role for NO/cGMP signaling in the development of high IOP. We hypothesize that an increase in IOP is triggered by a reduction in NO/sGC/cGMP signaling in the ciliary muscle and the trabecular meshwork, resulting in the contraction of the angle and reduction in aqueous outflow. To date, only one spontaneously-occurring murine model of glaucoma has been described (aging DBA/2J mice). However, the molecular mechanism underlying this phenotype is unknown. The availability of sGCα 1-/- mice with high IOP represents a novel and unique model of glaucoma and represents an outstanding opportunity to gain novel insights into the pathogenesis of glaucoma. We furthermore believe that these collaborative studies may enable rapid application of existing therapeutic compounds that alter NO/cGMP signaling to the treatment of glaucoma or may provide the scientific foundation for the development of new therapeutic approaches to the most common cause of blindness in the US.

Indications for Emergent Magnetic Resonance Neuro-Imaging in Emergency Department Patients with Dizziness- A Prospective Pilot Study

Principal Investigator: Maureen Chase, MD, Beth Israel Deaconess Medical Center

Co-Investigator(s): Marc Camacho, MD, Beth Israel Deaconess Medical Center
Jonathan Edlow, MD, Beth Israel Deaconess Medical Center
Joshua Goldstein, MD, PhD, Massachusetts General Hospital
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Magdy Selim, MD, PhD, Beth Israel Deaconess Medical Center

An estimated 30% of patients with dizziness will have a serious cause for their symptoms. Prior studies suggest that the cause with the most potential for missed diagnosis with serious consequence is acute stroke. We hypothesize that a series of distinct clinical characteristics will be present in patients at risk for an acute cerebrovascular event. We support this hypothesis by preliminary retrospective data identifying several clinical factors associated with a cerebrovascular cause for dizziness. This a problem in dire need of focused research because:1. Dizziness is a common ED complaint with many serious causes creating a complex decision-making process; 2.There is considerable practice variability with no established guidelines for emergent management; 3.The cost of a missed cerebrovascular event is high; 4.There is opportunity to better focus healthcare resources toward those at highest risk without compromising patient safety and care. Specific Aim: To prospectively identify characteristics associated with a cerebrovascular event in ED patients with dizziness. We will prospectively enroll an unselected cohort of ED patients with dizziness, examine all clinical features associated with their ED visit and report rates of all clinically serious and emergent causes. Covariates will be analyzed via logistic regression to identify those associated with the primary outcome of acute cerebrovascular event. The longterm goal of this pilot project is to develop a clinical decision rule for proper identification of this high risk group. We will assess the predictive validity of the rule for identifying patients at highest risk of cerebrovascular event in whom emergent MRI is indicated.

eCARE: The New Generation of Epidemiologic Studies

Principal Investigator: Jorge Chavarro, MD, ScD, Brigham and Women's Hospital

Co-Investigator(s): Matthew Gillman, MD, SM, Harvard Pilgrim Health Care/DPM
Richard Platt, MD, SM, Harvard Pilgrim Health Care/DPM
Meir Stampfer, MD, DrPH, Brigham and Women's Hospital
Walter Willett, MD, DrPH, Harvard School of Public Health

Prospective cohort studies have been successful in identifying a variety of lifestyle and biological risk factors for chronic diseases, many of which have been translated into clinical applications. However, devoting a substantial amount of resources towards validation of self-reported clinical outcomes and/or confirmation of outcomes through review of medical records is essential to maintain high quality data. At the same time, studies based on large electronic datasets originally collected for clinical, insurance claim or other purposes (e.g. national disease registries) have also been useful research tools allowing the passive follow-up of very large populations with high quality data on clinical outcomes. However, these studies often lack the richness of lifestyle and biological exposure data of prospective cohorts. Through eCARE (epidemiological and Clinical Alliance for Research Excellence) we propose to develop the new generation of epidemiologic studies by combining traditional design elements of exposure data collection of prospective cohort studies with the follow-up and clinical outcome confirmation strategies used in studies based on electronic databases. We propose to approach women aged 18-44 from the population insured by Harvard Pilgrim Health Care to address the following aims. 1) To evaluate the feasibility of enrolling a cohort through an insurance provider using internet-based assessment of lifestyle exposures. 2) To evaluate the 6-month active and passive follow-up rate of an internet-based cohort. 3) To evaluate the effectiveness of this research strategy to rapidly identify clinical outcomes using a combination of insurance claim and electronic medical record data.

Postoperative Pain After Pediatric Umbilical Hernia Repair: A Randomized Clinical Trial of Ultrasound-Guided Bilateral Rectus Sheath Blocks Versus Local Anesthetic Infiltration

Principal Investigator: Catherine Chen, MD, MPH, Children's Hospital Boston

Co-Investigator(s): Robert Dingeman, MD, Children's Hospital Boston

Recent studies on adult patients' perceptions of their hospital care have shown that improvements are needed in pain management. Regional anesthetic techniques that block specific peripheral nerves in adult patients have been increasingly used in recent decades as an alternative to general anesthesia or to decrease opioid use during and after surgery. Decreased postoperative complications have been observed, with fewer ambulatory patients requiring prolonged recovery room stays and/or unplanned hospital admissions. Regional anesthetic techniques have not been widely performed in pediatric patients because of the challenge in requiring children to report paresthesias during needle placements. However, pediatric anesthesiologists have recently begun to use ultrasound to identify anatomy, and to guide needle insertion and local anesthetic infiltration, thereby enabling peripheral nerve blocks to be performed safely in children under general anesthesia. To date, few studies have explored whether ultrasound-guided regional blocks of the abdomen in children have the desired outcome of reducing postoperative pain and/or decreasing opioid use. We propose a prospective, randomized, single-blinded study comparing the use of ultrasound-guided bilateral rectus sheath blocks to local wound infiltration in a pediatric population undergoing umbilical hernia repair at Children's Hospital Boston. Postoperative pain will be assessed using two validated patient- and parent-reported pain scores. Total opioid and non-opioid analgesic consumption will be monitored during the first 24 hours after surgery. Future studies may extend the use of regional abdominal pain blocks to other populations of pediatric general surgical patients undergoing laparoscopic surgery.

Understanding the Glioblastoma Genome

Principal Investigator: Clark Chen, MD, PhD, Dana-Farber Cancer Institute

Co-Investigator(s): Lynda Chin, MD, Dana-Farber Cancer Institute
Stephen Elledge, PhD, Brigham and Women's Hospital
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Towia Libermann, PhD, Beth Israel Deaconess Medical Center

The genomic landscape of cancer cells harbors a vast number of genetic alterations including point mutations, small insertions/deletions, and chromosomal rearrangements. Exploring the differences between the mutational profile of cancer and normal cells is a promising strategy for therapeutic development. However, the data from several large-scale DNA sequencing efforts suggest that most mutations uncovered are biologically inert. Studies of gene function that afford distinction between these “bystander” mutations from the “driver” mutations that actively contribute to carcinogenesis are of central importance in therapeutic development. The discovery of gene specific silencing through small interference (siRNA) or hairpin RNAs (shRNAs) has greatly accelerated the study of gene function. The availability of shRNAs directed against the entire human genome coupled with the development of methods for high-throughput screening enable functional studies on a genome scale. Such studies should provide a context for the identification of the “driver” mutations. Glioblastoma is the most common form of brain caner, with nearly uniform fatality for those afflicted. Recently, two large-scale sequencing efforts have yielded hundreds of mutations in genes that were not previously thought to be related to glioblastoma carcinogenesis. Without functional interrogation, the biologic meaning of these mutations remains unclear. We propose a genome-wide shRNA screen to identify genes essential for glioblastoma growth. The genes identified will be cross-referenced to mutations uncovered from the sequencing effort as a means to identify the subset of “driver” mutations. These candidate “driver” mutations will be subsequently validated using tissue culture as well as mouse xenograft and transgenic models.

Investigating Weight Disparities Among African-American and Black Youth in Cambridge: Research and Community Partners Gear-up for Intervention

Principal Investigator: Virginia Chomitz, PhD, Cambridge Health Alliance

Co-Investigator(s): Chandra Banks, EdM, Cambridge Public Schools
Ardene Goodridge, BA, Cambridge Area IV Neighborhood Coalition
Richard Harding, BS, Cambridge Health Alliance
Robin Harris, MEd, CAGS, Cambridge Public Health Department
Leroi Hicks, MD, MPH, Harvard Medical School
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Stephanie Shapiro Berkson, MPH, Cambridge Health Alliance
Joséfine Wendel, MS, RD, Cambridge Health Alliance

Background: In Cambridge, MA, as nationally, obesity among African American and Black (Black) youth is disproportionately high compared with other racial/ethnic groups. After five years of universal school-based interventions in Cambridge, body mass index (BMI) among children 5-14 years declined significantly. However, Black and Hispanic children experienced less significant reductions, which has initiated community action. Currently, there is scant evidence on effective interventions to reduce BMI disparities. Objective: To use community based participatory research (CBPR) to understand persisting BMI disparities among Black youth in Cambridge and to further inform intervention design that targets both the proximal and distal causes for these inequalities. Specific aims: 1) Explore the social, cultural, economic and environmental web of causality of childhood obesity among Cambridge Black youth. 2) Based on our findings, design a pilot intervention study to reduce BMI disparities. Methods: Building on preliminary secondary data analysis and in-depth interviews with community members, we will utilize mixed quantitative and qualitative methodologies, including: 1) parent-child dyad interviews and focus groups; 2) longitudinal analysis of school-based BMI dataset (2000-2007); Research Partners will meet twice with a community advisory board to review findings and guide intervention development. Research partners include multi-disciplinary researchers and community members from the Institute for Community Health, Cambridge Public Health Department, Harvard School of Public Health, Brigham and Women's Hospital, Cambridge Public Schools, Area Four Neighborhood Coalition, and the Boys and Girls Club.

The Impact of Bone Morphogenetic Protein on Outcomes and Costs of Spinal Surgery

Principal Investigator: Elizabeth Claus, MD, PhD, Brigham and Women's Hospital

Co-Investigator(s): Kevin Cahill, MD, PhD, MPH, Children's Hospital Boston
John Chi, MD, MPH, Brigham and Women's Hospital
Michael Groff, MD, Beth Israel Deaconess Medical Center
Kevin McGuire, MD, MS, Beth Israel Deaconess Medical Center

Back pain continues to be one of the leading causes of disability in the U.S. and is the most common reason for seeking evaluation by a physician, second only to the common cold. The treatment of back pain with spinal arthrodesis (fusion) has rapidly escalated over the past decade along with the development of fusion adjuncts such as recombinant bone morphogenetic protein (BMP). BMP promotes osteo-induction and has been applied during surgery to improve the process of spinal fusion. BMP is now utilized in an estimated 25% of spinal fusions nationally with usage increasing each year in all categories of fusion. The costs to the healthcare system associated with BMP use are significant; BMP increases procedural costs by as much as 40% and over 3 billion dollars has been spent on this product in the last 5 years. Furthermore, the clinical indications for use are not defined and wide regional variation in utilization exists. The goal of this pilot study is to form a collaborative group consisting of neurosurgeons, orthopedic surgeons, and epidemiologists to analyze the influence of novel spinal technologies on the outcomes and costs of surgical treatment of back and neck pain. The specific aim of the pilot project will be to perform a longitudinal population-level analysis of BMP use with a focus on the specific outcomes of prevention of revision procedures and post-operative resource utilization. This data will then be synthesized with cost data in a decision-analytic model to formulate usage guidelines for specific fusion procedures and identify areas for focused clinical trials of efficacy.

Sexual Health Needs of Male Sex Workers in Ho Chi Minh City, Vietnam

Principal Investigator: Donn Colby, MD, MPH, Beth Israel Deaconess Medical Center

Co-Investigator(s): Matthew Mimiaga, ScD, MPH, Massachusetts General Hospital

This project is a collaborative effort between the Fenway Institute, which has extensive experience in addressing the health needs of men who have sex with men (MSM), including high-risk subgroups such as male sex workers (MSW), and the Harvard Medical School AIDS Initiative in Vietnam (HAIVN), which has provided training on the clinical care of HIV/AIDS in Vietnam since 2003. The aim is to conduct formative research to better understand risk and protective factors for HIV/STI transmission among MSW in Ho Chi Minh City. MSW have been recognized as a high-risk group for HIV/STI in Vietnam, but there has been no previous research about the population and there are no programs which specifically target MSW for HIV/STI prevention. In the first phase, we will conduct qualitative interviews with MSW to better understand local terminology, cultural factors, reasons for engaging in sex work, HIV risk dynamics, barriers and facilitators of HIV testing/care, and will describe in more detail beliefs about HIV/STI risk. Second, we will use the information gained through the qualitative interviews to design a larger, culturally responsive, quantitative assessment. The quantitative assessment will determine risk behaviors, including sexual risk in the context of sex work and with non-commercial sexual partners, knowledge and beliefs about HIV/STI transmission and prevention, protective factors, and other psychosocial and health variables. Baseline HIV/STI prevalence data will also be collected. Ultimately, we will use these findings to develop a proposal for a specific intervention designed to decrease HIV/STI risk behavior among MSW in Vietnam.

Investigating Sodium Dynamics in Human Heart Disease

Principal Investigator: Saumya Das, MD, PhD, Massachusetts General Hospital

Co-Investigator(s): Heather Clark, PhD, Charles Stark Draper Laboratory
Federica delMonte, MD, PhD, Beth Israel Deaconess Medical Center

The voltage-gated sodium channel SCN5a determines the depolarization phase of the cardiomyocyte action potential. SCN5a dysfunction can lead to alterations in the shape and duration of the action potential, and secondary alteration in calcium handling, which manifests clinically as pro-arrhythmia and cardiac dysfunction. While inherited mutations in SCN5a have been associated with arrhythmias and cardiomyopathy, acquired cardiac disorders such as ischemic or dilated cardiomyopathies have been recently associated with alteration of SCN5a function. However, imaging of single cardiomyocyte sodium dynamics in human cardiomyopathies has not been explored due to the lack of suitable fluorescent sodium indicators. This grant proposes a collaborative effort to determine how sodium dynamics are altered in human cardiomyopathies. Our co-investigator Dr. Clark has developed and validated novel sodium-sensitive fluorescent nanosensors, the optical properties of which allow for high resolution spatial and temporal imaging of sodium dynamics at the single cell level, while our co-investigator Dr. del Monte has 20 years expertise in isolating viable and functional adult cardiomyocytes from explanted human hearts. Sodium-sensitive nanosensors will be injected into adult cardiomyocytes isolated from explanted hearts from patients with cardiomyopathies or non-failing donor hearts unused for transplantation from individuals deceased from a non-cardiac cause. Using confocal microscopy and high-speed image acquisition sodium fluxes will be visualized, and acquired data will be analyzed to determine how sodium dynamics are spatially and temporally altered in human disease. These experiments will provide insight into an important biologic process as well as avenues for developing novel therapies in heart failure patients.

Improving Fitness in Adolescents at Increased Cardiometabolic Risk: Piloting an Interactive Fitness Program

Principal Investigator: Sarah de Ferranti, MD, MPH, Children's Hospital Boston

Co-Investigator(s): Scott Crouter, MS, PhD, University of Massachusetts Boston
Laura Hayman, MSN, PhD, University of Massachusetts Boston
Stavroula Osganian, MD, MPH, ScD, Children's Hospital Boston
Jessica Whiteley, MS, PhD, University of Massachusetts Boston

Childhood obesity is increasingly common and is predictive of adult type 2 diabetes and cardiovascular disease (CVD). Recent pediatric studies suggest exercise reduces cardiometabolic risk factors. Despite evidence of its benefits, exercise training prescribed by pediatricians is traditionally vague, developmentally inappropriate, and/or fraught with psychological, financial and practical barriers. There has been recent interest in the use of interactive technologies as a way to translate known positive benefits of exercise into increased physical activity in youth. Initial adult studies demonstrate benefits, yet there are few studies of exer-gaming involving children at increased CVD risk. This proposal involves a partnership between Children's Hospital Boston and the GoKids Boston Youth Fitness Research and Training Center at UMass Boston, featuring an interdisciplinary team of researchers and clinicians from pediatric cardiology, prevention, nursing, exercise physiology, and behavior change. The pilot project seeks to utilize a state-of-the-art exercise training facility incorporating the latest technology-based exercise games ("exergames") to evaluate effects in Boston Public School elementary children on levels of moderate or vigorous physical activity (MVPA), as well as CVD risk factor levels, cardiorespiratory fitness, body composition and quality of life pre and post intervention and compared to an Advice-Only condition. This data will demonstrate the efficacy of an innovative exercise program in increasing MVPA, and suggest whether this increase improves fitness and favorably modifies cardiovascular risk factors in high-risk inner-city school children. The results of this pilot study can be used to support a larger scale community-based effectiveness trial of technology-supported physical activity for children.

An Exposure Biomarker for Effect of Biomass Particulate Matter Pollution on Child Pneumonia

Principal Investigator: Majid Ezzati, PhD, Harvard School of Public Health

Co-Investigator(s): Lester Kobzik, MD, Harvard School of Public Health

One half of the world's population uses biomass fuels and coal for cooking and heating. Burning unprocessed biomass emits high concentrations of multiple hazardous pollutants, including fine particles (PM2.5), which are considered the best indicator of hazardous effects of combustion products. Infants and children exposed to biomass smoke have an increased risk of pneumonia and possibly other respiratory infections. It has been hypothesized that biomass smoke exposure causes pneumonia by impairing the function of pulmonary alveolar macrophages (AMs), an important defense mechanism against bacteria. Our ability to investigate the effects of biomass smoke exposure and interventions on infectious diseases is severely constrained by a lack of reliable exposure markers. The objective of our cross-disciplinary catalyst research is to identify and test a reliable biomarker for exposure to biomass smoke PM2.5. The candidate marker is the density of (black) elemental carbon (BC/EC) in AMs. We will measure the exposure of 15-20 children to PM2.5 emitted from burning of biomass fuels in their homes, and determine the proportion PM2.5 mass that is EC. We will then quantify the association of children's exposure to EC and total PM2.5 with BC density in AMs obtained from induced sputum samples. Data will be collected in The Gambia, where we have established research collaborations with the MRC Laboratories. The identification and validation of a reliable biomarker for measuring PM exposure will provide an essential tool for epidemiologic studies; focus on macrophages will help develop hypotheses for research on the mechanisms of pollution-infection effects.

Imaging Breast Tumors with Diffuse Optical Imaging and Harmonic Compression

Principal Investigator: Qianqian Fang, PhD, Massachusetts General Hospital

Co-Investigator(s): Stefan Carp, PhD, Massachusetts General Hospital
Steven Isakoff, MD, PhD, Massachusetts General Hospital
Michelle Specht, MD, Massachusetts General Hospital

Breast cancer accounts for 15% of cancer deaths in US women and ranks second among all cancers. While X-ray based mammography has been widely used for breast screening, it has shown a low specificity which results in a large number of unnecessary biopsies. Investigating functional imaging contrast becomes increasingly important to improve specificity. Recent advances in diffuse optical imaging have revealed high specificity for the presence of breast tumors based on water and hemoglobin concentrations. Studies with fixed-separation breast compression also suggested the potential diagnostic values of tissue hemodynamics measured with optical imaging. In this study, we combine the strengths of these findings and target at further improvement in specificity by developing functional dynamic biomarkers with higher robustness. We hypothesize that 1) a gentle harmonic (cyclic) compression can enhance the vascular, mechanical and tissue chromophore contrasts in the tumor and produce dynamic biomarkers with high specificity; 2) the compression at various frequencies effectively separates noisy tissue transients from the steady-state response, leading to significantly more reliable dynamic biomarker quantification. To test these hypotheses, we propose to 1) develop a breast imaging system to perform high-speed optical imaging during speed-adjustable harmonic breast compression, 2) develop algorithms to perform difference imaging and frequency-domain analysis to quantify functional hemodynamic parameters from the measurement; 3) to evaluate these biomarkers by measuring healthy and tumor-bearing breasts and identify the imaging contrast. This proposal has the potential to uncover a set of robust imaging biomarkers that may lead to more accurate diagnosis of breast cancer.

Translational Research on *Trichomonas vaginalis* Viruses – an Interdisciplinary Approach

Principal Investigator: Raina Fichorova, MD, PhD, Brigham and Women's Hospital

Co-Investigator(s): Max Nibert, PhD, MD, Harvard Medical School

This interdisciplinary study concerns critical gaps in our understanding of the mucosal immune defenses of the female genital tract and trichomoniasis, the most common non-viral sexually transmitted infection in the world. Trichomoniasis is caused by protozoan parasite *Trichomonas vaginalis* (TV). It is linked to increased incidence of HIV and HPV transmission, pre-term delivery, low birth weight, cervical cancer, vaginitis, and pelvic inflammatory disease. African-American women suffer highest prevalence and complication rates. The pathogenesis is poorly understood. The parasite can carry dsRNA viruses (TVVs) but little is known about their genetics, and virtually nothing is known about their relevance to the host inflammatory reaction. We have identified the simultaneous presence of TVVs of three distinct genotypes in a TV isolate from a woman with acute vaginitis. Furthermore, our preliminary results show that in human vaginal epithelial cells TV strains harboring one or more TVVs induce a heightened inflammatory response in comparison to TVV-free strains. We hypothesize that TVVs evade the vaginal mucosal immune system via regulating parasite genes or via direct interaction with host cell receptors and signaling pathways. Our aims are to: 1) identify molecular determinants of TVV–host interaction with impact on vaginal mucosal immunity, and 2) establish related genetic-molecular characteristics of TVV. The approach includes a physiologic *in-vitro* model system and a variety of molecular biology techniques and tools. Our study will identify new targets for novel diagnostics, therapies and prevention strategies that can curb TV-related devastating social, economic and medical burdens, especially for women and children.

A Pilot Clinical Study to Evaluate the Effects of a Vascular Endothelial Growth Factor (VEGF) Inhibitor as an Adjunctive Treatment to Photoangiolysis in Patients with Bilateral Recurrent Respiratory Papillomatosis of the Vocal Folds

Principal Investigator: Mason Freeman, MD, Massachusetts General Hospital

Co-Investigator(s): Robert Hillman, PhD, Massachusetts General Hospital
Steven Zeitels, MD, Massachusetts General Hospital

Recurrent respiratory papillomatosis (RRP) is characterized by the proliferation of squamous papillomas in both children and adults. As no curative therapy is available, repeat surgical resections and antiviral medication are used to maintain airway patency. Over time, these treatments commonly result in scarring and severely diminished vocal functions. Angiogenesis plays an important role in the growths of papillomas. It was hypothesized that inhibiting vessel formation might therefore ameliorate RRP. Preliminary results of treatment with laser surgery and injection of a VEGF inhibitor, bevacizumab (Avastin®), into diseased vocal folds in 10 adult patients with bilateral RRP at the MGH Voice Center were promising. After 4-5 injections, no patient has required microlaryngeal surgery with general anesthesia and all have had substantial improvement in vocal functions. The Translational Medicine Group, working in collaboration with the MGH Voice Center propose to 1) develop methods to quantify RRP recurrence and ablative surgery requirements using still images taken from transoral or transnasal video strobolaryngoscopy, 2) design and conduct a pilot clinical study in 20 patients in which blinded therapy using bevacizumab injections in one vocal fold will be compared to placebo injections in the contralateral fold, 3) establish clinical endpoints that can be tested in a prospective, multi-center, double blind, placebo controlled trial to demonstrate the efficacy of laser surgery and adjunctive bevacizumab treatment. Successful completion of the pilot study with favorable results will provide the preliminary data required for a full phase 2b study grant application to the NIDCD.

Magnetic Resonance Enterography as a Noninvasive Method to Assess Disease Severity and Activity in Pediatric Crohn's Disease

Principal Investigator: Michael Gee, MD, PhD, Massachusetts General Hospital

Co-Investigator(s): Jeffrey Biller, MD, Massachusetts General Hospital
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Crohn's disease is a chronic relapsing bowel disorder affecting approximately 630,000 people in North America, with a significant prevalence within the pediatric population. CT enterography (CT-E) is currently the gold standard imaging modality for evaluating Crohn's patients due to its ability to detect both intrinsic bowel inflammation and extraintestinal complications; however, a significant limitation of CT is patient exposure to ionizing radiation. The potential risk of radiation-induced malignancy from imaging is an important consideration for Crohn's patients diagnosed during adolescence, who are likely to require frequent imaging over their lifetimes due to the episodic nature of the disease. Magnetic resonance imaging is an alternative imaging modality that provides superior soft tissue contrast to CT while avoiding ionizing radiation exposure; MR enterography (MR-E) is a specific MRI technique that combines enteric and intravenous contrast administration to detect intestinal pathology. The purpose of this prospective evaluation of imaging technologies is to determine whether MR-E can substitute for CT-E in the imaging evaluation of pediatric Crohn's patients, which would significantly reduce lifetime radiation exposure in this patient population. A second aim is to determine whether MR-E can provide an accurate evaluation of Crohn's disease activity and severity using a histologic reference standard. This would advance the role of imaging in the clinical management of Crohn's disease patients by aiding in treatment decision-making (medical vs surgical) as well as assessing early response to therapies.

An Intrapartum Rapid Test for Group B *Streptococcus*

Principal Investigator: Michele Hacker, ScD, MSPH, Beth Israel Deaconess Medical Center

Co-Investigator(s): Munish Gupta, MD, MMSc, Beth Israel Deaconess Medical Center
Brett Young, MD, Beth Israel Deaconess Medical Center

Background: Intrapartum neonatal exposure to Group B *Streptococcus* (GBS) can cause significant neonatal morbidity; thus, pregnant women are universally screened for GBS in the third trimester. The administration of prophylactic intrapartum antibiotics is based on this early screening test. However, GBS is known to have a transient colonization period such that the test's sensitivity can be as low as 52%. Intrapartum GBS testing was impossible before the recent introduction of a rapid assay. Objective: The objective is to evaluate whether a rapid GBS assay in the intrapartum period has superior sensitivity, specificity and predictive values than the early screening test and to assess the influence on neonatal outcomes. Methods: All adult laboring term patients with third trimester GBS culture results will be eligible. Women who consent will have two recto-vaginal swabs performed before antibiotics are administered. One swab will be used for the rapid assay and the other for culture. We anticipate enrolling 390 women to have 80% power to detect a 7% difference in sensitivity, while allowing for failed test results and loss to follow up. Outcome: The primary outcome is sensitivity of the rapid GBS assay, which will be compared to antepartum culture sensitivity. The intrapartum culture will be the gold standard for both tests. Secondary outcomes include specificity, predictive values, neonatal intensive care admissions, infections and sepsis evaluations. Findings could influence clinical practice and result in more appropriate treatment to protect neonates, particularly preterm infants delivered before third trimester screening, from the risks of intrapartum GBS exposure.

The Regulation of Fatty Acid Metabolism by PML and SIRT3

Principal Investigator: Marcia Haigis, PhD, Harvard Medical School

Co-Investigator(s): Pier Paolo Pandolfi, MD, PhD, Beth Israel Deaconess Medical Center

PML is the central component of a nuclear structure termed nuclear body, which is critical in the response to stress insults. Loss of PML results in enhanced survival, abolishment of senescence and cancer progression. Moreover, a fraction of PML localizes to the cytoplasm where its functions remain poorly understood. Through the metabolic characterization of PML knockout mice and cells we have discovered a novel function of PML in nutrient adaptation. PML plays a role in the hepatic fasting response and indeed PML null cells exhibit decreased fatty acid oxidation. In addition, PML null mice are predisposed to obesity in conditions of high fat diet. Mechanistically, we have screened for interactions of PML and the seven mammalian sirtuins, a family of proteins implicated in the regulation of metabolism, stress resistance and longevity. We found an exquisitely selective binding of PML to the mitochondrial sirtuin SIRT3, which regulates the acetylation status of numerous mitochondrial beta-oxidation enzymes. Thus, we propose that PML and SIRT3 function together outside the nucleus to fine-tune lipid metabolism and the response to nutrient adaptation. To test this hypothesis we will develop the following specific aims: 1) to study the impact of the interaction of PML and SIRT3 in the acetylation and activity of components of the beta-oxidation pathway 2) to ascertain the effect of the novel PML-SIRT3 pathway on PML acetylation as well as PML and SIRT3 localization and 3) to analyze the consequences of compound PML and SIRT3-loss *in vivo* on lipid metabolism in fasting and diet-induced obesity.

The Relationship Between Defects in Mucosal Innate Immunity and Abnormalities in the Microbial Community of Patients with Refractory Chronic Rhinosinusitis

Principal Investigator: Daniel Hamilos, MD, Massachusetts General Hospital

Co-Investigator(s): Eric Holbrook, MD, Massachusetts Eye and Ear Infirmary
Stephen Lory, PhD, Harvard Medical School

Our goal is to study patients with refractory chronic rhinosinusitis (CRS) who experience repeated sinus infections with Staphylococcus aureus or enteric Gram-negative bacteria despite normal systemic immune function. We wish to explore the relationship between defects in mucosal innate immunity and abnormalities in the microbial community of these patients. Refractory CRS comprises only 6.7% of our patient population. We will recruit 8 patients based on an operational definition of refractory CRS (as above). Dr. Holbrook will obtain 3 sinus tissue biopsies per patient. Through the Advanced Tissue Resource Center, we will perform laser capture microdissection on one biopsy to isolate the epithelial and glandular compartments. Through the Partners Center for Personalized Genetic Medicine we will obtain an mRNA expression profile on each compartment using microarray. We will recruit and biopsy 8 adult healthy controls as a comparison group. Genes that are differentially expressed will be investigated further using RT-PCR on the same tissues. Dr. Lory will assist in analyzing the microbial community in each subject. We will isolate DNA from an en bloc (with attached mucus) tissue biopsy, use PCR to amplify bacterial-specific 16S RNA, randomly clone 96 of the PCR products into E coli and sequence the strain-specific segments corresponding to the variable portion of the 16S RNA gene to identify the specific bacterial phylotypes. Preliminary associations between defects in innate immunity and differences in the microbial community will be analyzed in order to set up testable hypotheses regarding the impart of particular innate defects on the microbial community.

Mechanisms of Hypertension in Patients Treated with Anti-angiogenic Chemotherapies

Principal Investigator: Benjamin Humphreys, MD, PhD, Brigham and Women's Hospital

Co-Investigator(s): Toni Choueiri, MD, Dana-Farber Cancer Institute
Gary Curhan, MD, ScD, Cambridge Health Alliance
Ananth Karumanchi, MD, Beth Israel Deaconess Medical Center
Javid Moslehi, MD, Brigham and Women's Hospital
Emily Schopick, MD, MPH, Brigham and Women's Hospital

Anti-angiogenic chemotherapies are a very promising new class of FDA-approved drugs that act in part by blocking vascular endothelial growth factor (VEGF) signaling. Severe hypertension, resembling the clinical syndrome of pre-eclampsia, has emerged as an important and unexpected toxicity of this drug class. Very recent data suggests that patients developing severe hypertension while on anti-angiogenic therapy have a superior anti-tumor response, suggesting that hypertension may be a biomarker for effective *in vivo* VEGF blockade. The mechanisms underlying anti-angiogenic therapy-induced hypertension, and why this may correlate with anti-tumor efficacy, are not understood. We hypothesize that hypertension in these patients reflects a blockade of VEGF-induced vasodilation. We will test this hypothesis by measuring the activity of endothelial nitric oxide synthetase and prostacyclin activity, two vasodilatory pathways regulated by VEGF. We will measure the levels of NO and prostacyclin metabolites over time in blood and urine before and after initiating anti-angiogenic therapies in 20 patients, half of whom will be selected because they have developed hypertension upon treatment. We predict that levels of these biomarkers will inversely correlate with blood pressure, and that patients with the most dramatic suppression will have the best tumor response. These important studies will (1) direct anti-hypertensive therapy choice for anti-angiogenic therapy-induced hypertension (ie direct vasodilators), (2) validate new biomarkers of inhibited VEGF activity in humans potentially linked to a clinical outcome, (3) establish a protocol for assessing future, novel biomarkers of VEGF blockade, and (4) point to an underappreciated role for VEGF-mediated vasodilation in both essential hypertension and pre-eclampsia.

Development of a Robust Primary Cell Culture System for Acute Lymphoblastic Leukemia

Principal Investigator: Tan Ince, MD, PhD, Brigham and Women's Hospital

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It is extremely difficult to grow cells from primary human tumors in cell culture. Ironically, this limitation extends even to liquid phase tumors such as acute lymphoblastic leukemias (ALL), which usually fail to expand *ex vivo* and from which relatively few lines have been established. Overcoming this limitation through development of reliable cell culture conditions for short- and long-term growth would represent a significant advance; if robust, such a system could permit preclinical trials of therapeutics to be conducted on primary cells in culture instead xenografts, which are both costly and time consuming, and perhaps even enable drug testing to be performed routinely on all tumors in the future. This project brings together pathologists and adult and pediatric oncologists focused on cancer pathophysiology and therapeutics. The PI through systematic analysis has developed a completely defined, serum-free cell culture medium that permits the reliable *ex vivo* expansion of primary human epithelial cancers, such as ovarian carcinoma, for over 40 doublings. We will build on these successes to develop a robust cell culture system for acute lymphoblastic leukemia, starting with primary human T-ALLs expanded in immunodeficient NOG mice. Using this standardized set of input cells, we will systematically test variables (e.g., growth factors, feeder cells, and O2 tension) until we arrive at conditions that permit expansion. Once established, we will determine the doubling limit (if any), and explore the effects of *ex vivo* cultivation on expression profiles and the ability to reinitiate tumors in immunodeficient mice.

Anti-inflammatory Prodrug-based Hydrogels as Novel Therapeutic and Formulations for Treatment of Arthritis

Principal Investigator: David Lee, MD, PhD, Brigham and Women's Hospital

Co-Investigator(s): Jeffrey Karp, PhD, Brigham and Women's Hospital

HYPOTHESIS: We hypothesize that pro-drug based hydrogels represent both a novel therapeutic option for treatment of inflammatory arthritis as well as a powerful research tool for examination of disease mechanisms. SPECIFIC AIMS: Aim 1) Examine prodrug-based gel dissolution in healthy and arthritic mouse joints; Aim 2) Assess prodrug-based gel therapeutic potential using compounds with known efficacy; Aim 3) Utilize prodrug-based gel matrices to explore systemic vs local involvement of sPLA2 in inflammatory arthritis. We have devised a novel method of controlled drug delivery based on self-assembly of low-molecular-weight pro-drug gelators. By designing prodrug-based nano-fibrous gels, we envision a capacity for delivery of high concentrations of locally released therapeutic compounds while avoiding systemic toxicity. Hydrogel polymers have been previously applied as intelligent carriers in controlled drug-delivery systems. However, their application has been limited by low drug encapsulation efficiency and insufficient sustained release of drugs. Further, current hydrogel formulations fragment easily leading to drug release which precludes their use in the high strain context of diarthrodial joints. Our gel design utilizes prodrug as a central component by including key functional groups that can promote self-assembly in aqueous solutions. These gel formulations are highly stable *in vitro* even in the context of substantial shear forces. To accomplish disassembly (and thus therapeutic delivery), prodrug is susceptible to metabolism by enzymes present in the tissue milieu, thereby delivering the therapeutic compound. Indeed, in our approach, prodrug degrades into pure drug with a single non-cytotoxic fatty acid upon enzyme mediated matrix degradation. Interestingly, this approach provides an opportunity to avoid the undesired burst release that is often the hallmark of polymer-based drug- delivery devices. Further, by including hydrophobic therapeutic compounds during the assembly process, one can develop delivery vehicles for multiple drugs. Overall, the prodrug-based gel approach is particularly attractive in the context of arthritis, where the diseased joint cavity provides a readily accessible ‘depot’ for placement of time-release compounds.

Culture-independent Analyses of Pediatric Nostril and Nasopharynx Microbiota

Principal Investigator: Katherine Lemon, MD, PhD, Children's Hospital Boston

Co-Investigator(s): Jonathan Finkelstein, MD, MPH, Harvard Pilgrim Health Care/DPM
Roberto Kolter, PhD, Harvard Medical School
Grace Lee, MD, MPH, Harvard Pilgrim Health Care/DPM

The upper respiratory tract can be colonized by pathogens whose carriage increases the risk for infection. Why some individuals carry pathogens and others do not, remains a mystery. While this might be related to host genetics or exposure risks, we propose that pathogen carriage is related to the composition of upper respiratory tract microbiota. To test this hypothesis, we must first completely characterize the bacterial communities of the upper respiratory tract of healthy children. The recent application of culture-independent analyses to the mouth, gut, skin, and vagina has revealed that hundreds of bacterial species colonize these niches. The surfaces of the upper respiratory tract, in contrast, remain largely unexplored by culture-independent approaches. We will comprehensively characterize nostril and nasopharyngeal microbiota composition in healthy children under 7 years old using tag pyrosequencing of bacterial 16S rRNA gene variable regions. Our samples will be mucosal swabs that, along with paired clinical and epidemiologic data, were collected in a separate culture-based study of specific pathogen carriage in children. We will correlate microbiota composition with factors associated with increased risk for pathogen carriage and bacterial infection, such as childcare attendance, antibiotic use and viral infection. This research is innovative both in the use of new technologies and its multidisciplinary nature. This work relates directly to clinical care and population health in the context of the rapid rise of community acquired pathogens, such as MRSA, and our continuing perturbations of human microbiota through immunization and high rates of antibiotic use.

Novel Inhibitors of *Chlamydia* Infection

Principal Investigator: Cammie Lesser, MD, PhD, Massachusetts General Hospital

Co-Investigator(s): Stephen Lory, PhD, Harvard Medical School

The yeast *Saccharomyces cerevisiae* is a common model system used to study basic conserved eukaryotic cellular processes. Our work has established that yeast are also a powerful model system to study interactions between bacterial pathogens and host cells. This system is particularly useful for studying virulence proteins that bacteria directly inject into host cells as these virulence proteins often target cellular processes conserved among eukaryotes. We recently used this system to identify the first essential virulence protein from *Chlamydia pneumoniae*. Remarkably, we observe that expression of *C. pneumoniae* CopN in both yeast and mammalian cells results in growth inhibition due to a cell cycle arrest associated with the disruption of microtubules. A screen of a small molecule library resulted in the identification of two active compounds that inhibit CopN activity in yeast. These compounds also remarkably inhibit *C. pneumoniae* replication in mammalian cells. Thus, we have developed two new lead compounds for the development of therapeutics targeted against *C. pneumoniae*, a major human pathogen that is associated with acute infections such as pneumonia as well as long-term sequelae including the development of atherosclerosis. We propose to exploit yeast functional genomic approaches to determine the mechanism by which CopN disrupts microtubules and confer a cell cycle arrest. Studies targeted towards understanding CopN function as well as in identifying the ways that the small molecules inhibit its activity will provide important insights into the potential utility of further use of our lead compounds towards the development of new anti-Chlamydial agents.

Mitral Valve Adaptation to Mechanical Stresses: Bioengineering Studies to Reduce Heart Failure

Principal Investigator: Robert Levine, MD, Massachusetts General Hospital

Co-Investigator(s): Elena Aikawa, MD, PhD, Massachusetts General Hospital
Joyce Bischoff, PhD, Children's Hospital Boston
Adam Feinberg, PhD, Harvard School of Engineering and Applied Sciences

Ischemic mitral regurgitation (IMR) is a common complication that doubles mortality after myocardial infarction (MI). IMR is caused by cardiac remodeling that restricts mitral valve (MV) closure – a mismatch between valve and chamber size. This project challenges previous assumptions that the MV is passive in IMR, with the goal of augmenting MV area therapeutically. The central hypothesis is that MV area increases with mechanical stretch by cell activation and matrix production. A corollary is that MI may independently alter MV adaptation by modifying cytokines and growth factors. Testing this hypothesis lies at the interface of bioengineering with cell and molecular biology. At Harvard SEAS, an original approach has been developed to study cells organized on thin-film substrates and subjected to controlled mechanical forces and soluble modulating factors. This system will be applied to determine how mechanical perturbation contributes to leaflet growth using cells from an *in vivo* model. *In vivo*, a cross-disciplinary team will study leaflet stretch both independently and combined with MI by retracting the MV attachments. In stretched vs control animals, MV area will be followed by 3D echo and correlated with cellular activation and matrix deposition. This project introduces a new way of thinking about how transduction of mechanical forces leads to biological effects. The bioengineering collaboration will allow a wide range of controlled variation in mechanical conditions and signaling environment. The results can potentially indicate new therapeutic avenues for this common disease condition.

***In Vivo* Detection of Brain Glutamate in Iraq and Afghanistan War Veterans Suffering from Traumatic Brain Injury**

Principal Investigator: Alexander Lin, PhD, Brigham and Women's Hospital

Co-Investigator(s): Kristin Heaton, PhD, US Army Research Institute of Environmental Medicine
Nirmal Keshava, PhD, Charles Stark Draper Laboratory
Wald Lawrence, PhD, Massachusetts General Hospital
Carolyn Mountford, PhD, Brigham and Women's Hospital

Mild traumatic brain injury (MTBI) affects over 1.4 million people each year, including 300,000 veterans of the Iraq and Afghanistan wars, and results in persistent cognitive and functional disorders whose long-term effects can be devastating. Glutamate is an important neurotransmitter, whose dysfunction has long been associated with MTBI, yet the use of glutamate antagonists has been hindered by the absence of reliable *in vivo* methods for measuring glutamate. BWH has developed novel methods of measuring brain glutamate using magnetic resonance spectroscopy (MRS), a non-invasive method of measuring *in vivo* chemical concentrations in the brain using widely available clinical MR scanners. One method is to acquire 1D MRS in the brain and utilize wavelet-based pattern recognition methods developed by Draper Laboratories to characterize biochemical markers of MTBI including glutamate. The second method utilizes a novel *in vivo* 2D MRS method which can accurately distinguish glutamate from other neurotransmitters. This method is most effective at high magnetic field strengths such as the 7 Tesla whole body MRI scanner available at the Martinos Center at MGH. We therefore propose to measure brain glutamate using these two methods in a small cohort of solders that have suffered from MTBI from the VA Hospital in Boston over a period of one year. This pilot data will provide the basis for a larger clinical study and also bring together the skills and resources of BWH, MGH, VA, and Draper Labs to tackle the single greatest medical problem facing our veterans today.

Childhood ADHD Registry

Principal Investigator: David Link, MD, Cambridge Health Alliance

Co-Investigator(s): James Perrin, MD, Massachusetts General Hospital

Attention Deficit Hyperactivity Disorder (ADHD) is a highly prevalent medical condition in the school-age pediatric population (7.8% for U.S.), and among the most idiosyncratically managed. This population is difficult to define; American Academy of Pediatrics guidelines are inadequately accepted; medication use is not systematic and yet on the rise; treatment results are scantily monitored. Preliminary data on 874 ADHD patients at Cambridge Health Alliance (CHA) indicate great variation in their management and gaps in standard process measures. Improving care for chronic childhood illnesses requires collaborative care planning and evidence-based guidelines. Registries that guide management and practice support methods have proven successful in improving outcomes for other conditions, like asthma. Our main research question is: Can an ADHD Registry improve behavioral health and academic indicators in children with ADHD? Our specific aims are to: 1) define the elements of an ADHD registry; 2) determine tools for outcome measures [e.g., behavioral ADHD tool, like Connors; academic grades/standardized tests] and significance levels for improvement; 3) pilot the registry for CHA patients and assess impact on chosen outcomes after 6 months as compared to a control group. To achieve our aims, we propose a novel collaboration with Massachusetts General Hospital (Pediatrics), Cambridge/Somerville Public Schools and Health Departments, parents, clinicians, IRB, and IT to construct a comprehensive ADHD Registry prototype. Data collected in this multi-center pilot will be used to determine the feasibility of turning the project into a large-scale clinical trial.

Ethical and Legal Controversies in End-of-Life Care for Heart Rhythm Patients

Principal Investigator: William Maisel, MD, MPH, Beth Israel Deaconess Medical Center

Co-Investigator(s): Dan Brock, PhD, Harvard Medical School
Aaron Kesselheim, MD, JD, MPH, Brigham and Women's Hospital
Daniel Kramer, MD, Beth Israel Deaconess Medical Center

Background: Permanent pacemakers (PM) and implantable defibrillators (ICDs) are clinically proven to improve survival in selected patients. Although more than 2 million patients enjoy the devices' benefits, surprisingly little research has addressed the ethical and legal aspects of end-of-life care for this population. Project Aims: This study is a collaboration among BIDMC Cardiovascular Institute, HMS Division of Medical Ethics, and BWH Division of Pharmacoepidemiology and Pharmacoeconomics. The specific aims of the study are to: 1) Understand and quantitatively measure heart rhythm device patient and physician ethical values and legal knowledge guiding end-of-life clinical care. 2) Quantitatively measure and analyze the clinical impact of patient-physician ethical and legal disagreements and misunderstandings. 3) Identify impediments to the delivery of ethical, legal, compassionate end-of-life care. Study Design and Methods: All patients with PMs and ICDs at BIDMC will be eligible for enrollment. A survey instrument will be developed and administered to patients and physicians to assess: 1) views on ethical and legal barriers to deactivating heart rhythm device functions, 2) perceptions of heart rhythm devices as compared to other life-sustaining therapies and interventions, 3) knowledge of state and federal regulations addressing patient and physician options at the end-of-life, and 4) impact of ethical views, legal knowledge, and study subject characteristics on delivery of patient care. Study Significance: The conclusions drawn from this study will help inform efforts at patient and physician education, refine the informed consent process, and provide a framework for future research and discussion on practice guidelines for patient management.

Neopharmacovigilence for Repositioning Medications

Principal Investigator: Kenneth Mandl, MD, MPH, Children's Hospital Boston

Co-Investigator(s): Mark Boguski, MD, PhD, Beth Israel Deaconess Medical Center

There are a number of remarkable examples of repurposed drugs whose additional (or replacement) indications were discovered serendipitously. As described in our upcoming Policy Forum in Science, we take a novel approach to this challenge, namely the repurposing of pharmacovigilance for drug and biomarker discovery. This approach capitalizes on recent advances in molecular medicine, human genomics, information technology and an increasingly sophisticated public eager for solutions to their unmet medical needs. Whereas the purpose of classical pharmacovigilance is to identify adverse side effects of drugs, we envision a new kind of pharmacovigilance (neo-pharmacovigilance) defined as the science and activities relating to the detection, assessment and understanding of beneficial side effects (or expanded indications) of drugs that may become apparent during their development or use. Type 2 pharmacovigilance could be carried using data-mining methods to look for potential beneficial events in electronic health records. To initiate a program to pilot test the feasibility of neo-pharmcovigilence using data from across the Harvard teaching hospitals, we will build upon prior work in which data from the Partners Healthcare research repository was used to uncover a dramatic population-level impact of COX-2 inhibitors on myocardial infarction; that study elucidated the potential role of health system data in the pharmaceutical life cycle, which we extend here. Classical pharmacovigilence requires creation, modeling, and validation of adverse event outcomes variables. Operationally, classical pharmacovigilance is carried out using defined methods, terminology and causality assessment criteria. The specific aims of this pilot grant are to develop conceptually similar methodologies and grounded approaches that will be necessary to enable type 2 pharmacovigilance for drug and biomarker discovery.

Analysis of Exhaled Volatiles for the Diagnosis of Invasive Aspergillosis and Other Invasive Fungal Disease

Principal Investigator: Francisco Marty, MD, Brigham and Women's Hospital

Co-Investigator(s): Lindsey Baden, MD, Brigham and Women's Hospital
Sophia Koo, MD, Brigham and Women's Hospital
Jose Trevejo, MD, PhD, Massachusetts Institute of Technology

Invasive aspergillosis (IA) and other invasive mold infections are associated with significant morbidity and mortality in immunocompromised hosts. Timely, accurate diagnosis with prompt initiation of appropriate antifungal therapy improves outcomes, but is difficult to achieve due to nonspecific clinical manifestations and the significant limitations of currently available traditional and culture-independent diagnostic modalities. *Aspergillus* and other invasive mold species produce unique, species-specific volatile metabolite signatures early in the course of invasion, and we hypothesize that detection of these volatile organic biomarkers in exhaled human breath can allow for earlier diagnosis than possible with currently available modalities. Our overall objective is to develop a novel, exquisitely sensitive differential mobility spectrometer (DMS)-based breath test for volatile organic compounds (VOCs) released early in IA and other invasive mold infections. If successful, we will have a noninvasive, simple, and highly sensitive assay (threshold of detection in the parts per trillion range) with a rapid turnaround time that can positively identify IA and other invasive mold infections that currently lack suitable early diagnostic modalities, such as Zygomycetes, Fusarium, and Scedosporium. Development of this novel methodology will ultimately allow better surveillance of high-risk patients, targeting of antifungal therapy, and improved patient outcomes. We aim to use Harvard Catalyst funding to construct a detailed repository of volatile compounds produced by *Aspergillus* species and a variety of other pathogenic molds at a series of biologically important time points in various *in vitro* growth conditions mimicking mammalian infection. We will also perform a small pilot study characterizing VOCs in the exhaled breath of patients with proven or probable IA.

A Novel Approach to the Assessment and Treatment of Suicide Risk in Depression

Principal Investigator: John Matthews, MD, MSc, Massachusetts General Hospital

Co-Investigator(s): Matthew Nock, PhD, Faculty of Arts and Sciences, Harvard University

Nearly one million people kill themselves worldwide each year, equaling one death by suicide approximately every 40 s. An enduring problem in the detection of suicidal patients is that clinical assessments rely almost exclusively on self-report of suicidal thoughts and intentions. Cognitive and social scientists recently have developed indirect, performance-based methods of measuring individuals' implicit thoughts about various constructs in ways that do not rely on self-report. One of these, Implicit Association Test, has been shown to have strong reliability, construct validity, and sensitivity to clinical change in treatment, and is resistant to attempts to "fake good". Dr. Matthew Nock (co-PI) has developed versions of the IAT that can distinguish between nonsuicidal persons, suicide ideators, and recent suicide attempters. A recent study of Dr. Nock's Suicide IAT (S-IAT) indicated that use of the S-IAT significantly improves the prediction of 6-month suicide attempts above and beyond the use of demographic, psychiatric, and clinician-prediction data. The proposed project seeks to: 1) to test an innovative performance-based tool (S-IAT) assessing patients' suicide risk at admission and discharge from an inpatient psychiatric unit while concurrently administering CBT and; 2) to determine the effectiveness of a brief suicide-specific CBT approach in treating suicidal thinking and behaviors in severely depressed patients requiring inpatient psychiatric hospitalization.

Expression of Left Ventricular 9p21 Variants in Diabetics

Principal Investigator: Jochen Muehlschlegel, MD, Brigham and Women's Hospital

Co-Investigator(s): Sary Aranki, MD, Brigham and Women's Hospital
Alessandro Doria, MD, PhD, MPH, Joslin Diabetes Center
Jonathan Seidman, PhD, Harvard Medical School

Multiple epidemiologic studies have documented a significant heritability for coronary artery disease (CAD), myocardial infarction (MI), and diabetes. Recent genome-wide association studies identified an association between cardiovascular disease or diabetes, with common genetic variants on chromosome 9p21. In addition, our proposed collaborator Dr. Doria has identified a synergism between these 9p21 variants and hyperglycemia on the risk of CAD. The consistency of the association of 9p21 genetic variants across several populations, along with the high frequency of the risk allele and the high proportion of patients with diabetes, makes this an important target for understanding the biological mechanism of cardiovascular disease and the effects of diabetes. We hypothesize that patients with variation in the 9p21.3 locus have altered left ventricular tissue mRNA transcription, and that the mRNA transcript differs in patients with and without diabetes and in their response to myocardial ischemia reperfusion injury. We are in the unique position to utilize a cross-disciplinary approach to investigate the genetic and biologic mechanisms of the interaction of diabetes with cardiovascular disease by combining the expertise of the Joslin Diabetes Center, the Departments of Genetics, the Division of Cardiac Surgery with the CABG Genomics Study program. Aim 1: We will collect left ventricular apical tissue before and after ischemic exposure during cardiopulmonary bypass and aortic cross-clamping in patients with and without diabetes. Aim 2: We will identify 9p21 transcripts that are differentially expressed or alternatively spliced in the tissue collected in Specific Aim 1 depending on the presence or absence of diabetes.

The Effects of Docosahexaenoic Acid on Periodontitis in Adults - A Pilot Randomized Controlled Trial

Principal Investigator: Kenneth Mukamal, MD, MPH, MA, Beth Israel Deaconess Medical Center

Co-Investigator(s): Roger Davis, ScD, Beth Israel Deaconess Medical Center
Max Goodson, DDS, PhD, The Forsyth Institute
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Thomas Van Dyke, DDS, PhD, MS, Boston University

Polyunsaturated fatty acids have been shown to have anti-inflammatory properties *in vitro* and *in vivo*. Periodontitis is a common, chronic inflammatory disease associated with major morbidity and is implicated as a risk factor for cerebrovascular disease and cancer. In a nationally representative sample of U.S adults, we found docosahexaenoic acid (DHA), a marine based omega-3 fatty acid, to be associated with a lower prevalence of periodontitis. Animal and *in-vitro* studies suggest that the protective effect of DHA on periodontitis and its complications is potentiated by aspirin and may be mediated through the reduction of cytokines involved in inflammation and bone homeostasis. We propose to harness the resources of the Harvard Catalyst funds to bring together epidemiologists, internists, dentists and biochemists from across Harvard to evaluate the effect of a potentially safer and less costly treatment for periodontitis. With one year of funding, we propose the four following aims: 1) investigate in 100 subjects whether DHA and low dose aspirin will improve periodontitis compared to low dose aspirin alone over a 3 month period based on clinical exam; 2) ascertain compliance through the measurement of plasma DHA; 3) evaluate potential mechanisms of action, including markers of inflammation, bone homeostasis and the targeted identification of key species of periodontal bacteria by quantitative PCR and chemifluorescent checkerboard DNA-DNA hybridization; 4) development of an NIH funded research program based on preliminary results.

Assessing Nutritional Consequences of Elevated Atmospheric Concentrations of Carbon Dioxide

Principal Investigator: Samuel Myers, MD, MPH, Faculty of Arts and Sciences, Harvard University

Co-Investigator(s): Noel Michele Holbrook, PhD, Faculty of Arts and Sciences, Harvard University
Walter Willett, DrPH, MD, Harvard School of Public Health

Climate change is expected to have wide-ranging impacts on human health. One impact that has not been well studied is the impact on human nutrition as a result of alterations in the nutrient composition of food crops. Numerous studies indicate that elevated levels of atmospheric carbon dioxide (CO_2) are associated with decreased concentrations of protein and micronutrients in the major grains and other food crops. Protein and micronutrient deficiencies are already responsible for significant burdens of disease globally. We propose to estimate the additional burden of disease from protein and micronutrient deficiencies associated with rising CO_2 levels. To do so, we will use published measurements of protein and micronutrient concentrations in different crop types in response to elevated levels of CO_2. We will use the United Nations Food and Agriculture (FAO) and other databases to establish the dietary source of protein and micronutrients for different target populations. Combining this information, we will estimate the impact of elevated CO_2 concentrations on total dietary intake of protein and micronutrients in these target populations. We will make preliminary estimates of the burden of disease that would be associated with these nutritional shifts for given levels of atmospheric carbon dioxide.

Development of a Point-of-care, High-throughput Microfluidic Technology to Isolate Circulating LAM Cells

Principal Investigator: Sunitha Nagrath, PhD, Massachusetts General Hospital

Co-Investigator(s): Elizabeth Henske, MD, Brigham and Women's Hospital

Lymphangioleiomyomatosis (LAM) is a rare multisystem disorder, characterized by a cystic lung disease with aberrant growth of smooth muscle-like cells. It is a sexist disease as it affects exclusively women, that too unfortunately in their child bearing years. Metastasis seems to be the mechanism by which the LAM cells disseminate. Metastatic LAM cells were identified in donor lungs transplanted to LAM patients. In addition, LAM cells have been detected in blood, chyle, and urine. Although a cellular link between the primary malignant disease and the peripheral metastases has been established in the form of circulating LAM cells (CLCs) in peripheral blood, a major challenge remains in deciphering the biology of this very unique cellular population, and ultimately, improving our systems level understanding and use these cells as biomarkers for diagnosis, prognosis and monitoring of response to a therapy. Furthermore, due to the lack of understanding of the molecular mechanisms involved in LAM, there is no known treatment yet for LAM, making it a disease with worst prognosis. The limitations are the unavailability of LAM specific cells, lack of sensitive isolation technologies to elucidate cellular and molecular mechanisms. Hence I would like to propose introducing a novel microfluidic technology for the reliable detection of circulating LAM cells from blood. An integrated technology and biology based approach will be adopted to address the efficient isolation and applications of CLCs. Specifically, a point-of-care, high-throughput microfluidic diagnostic CLC capture device will be developed for diagnosis and monitoring of LAM patients through disease course.

Modulation of the Reinforcing Strength of Cocaine by Sigma Receptor Antagonism

Principal Investigator: Jennifer Newman, PhD, McLean Hospital

Co-Investigator(s): Jack Bergman, PhD, McLean Hospital
Jonathan Katz, PhD, National Institutes of Health

Abstract withheld at the request of the investigator.

Genetic Modifiers of Cardiotoxicity: PILOT

Principal Investigator: Christopher Newton-Cheh, MD, MPH, Massachusetts General Hospital

Co-Investigator(s): Paul Arpino, PharmD, Massachusetts General Hospital
Peter Noseworthy, MD, Massachusetts General Hospital

Drug-induced QT prolongation and resultant potentially fatal arrhythmia is a costly impediment to drug development and an important issue of public safety. Current efforts to reduce the burden of arrhythmic cardiotoxicity are focused on identifying characteristics of the vulnerable drug that is predisposed to bind to the HERG potassium channel in the heart. However, identification of the vulnerable patient could have important public health implications. Electrocardiographic QT interval duration, a reflection of myocardial repolarization time, has a strong, graded relationship to sudden cardiac death, and has a substantial genetic underpinning (h2=0.35-0.45). Repolarization, and thus the QT interval, is regulated by redundant mechanisms. A single defect in one of these redundant pathways may remain subclinical until a second hit (e.g. drug exposure) unmasks the defect and results in altered repolarization and prolongation of the QT interval. We have recently shown that 14 common variants in ten genes influence inter-individual variability in QT duration (Newton-Cheh et al, Nature Genetics 2009). We hypothesize that in aggregate common genetic variants with strong effects on resting QT may predispose a subgroup of individuals to exaggerated prolongation of the QT in response to QT-prolonging medication. In the Harvard clinical research center, we propose to measure the change in QT interval following administration of oral moxifloxacin (a drug known to cause transient and mild QT prolongation) in individuals with and without QT-prolonging genotypes. These findings will serve as important preliminary data for an R01 to establish the relevance of common QT variants to cardiotoxic response in humans.

Boston Housing First: Evaluation of an Intervention to Decrease Homelessness and Improve Health

Principal Investigator: James J. O'Connell, MD, Massachusetts General Hospital

Co-Investigator(s): Earl Frances Cook, ScD, Harvard School of Public Health
Jill Roncarati, MPH, MPAS, Harvard School of Public Health

"Housing First" has swept the nation as a call to reduce chronic homelessness. In Boston, more than 200 homeless persons who receive care from the Boston Health Care for the Homeless Program (BHCHP) Street Team have moved into housing since 2000, most within the last 3-4 years. Although there has been an assumption that housing will lead to decreases in morbidity and mortality, there are currently no data that support this hypothesis. We propose forming a multi-disciplinary, cross-institutional collaboration between community-based practitioners at BHCHP and researchers from the Harvard School of Public Health to investigate whether housing the chronically homeless improves health outcomes and quality of life, decreases mortality, reduces health cost, and changes health utilization patterns. To do this, we aim to utilize data that are currently available on the housed group of 200 persons through the BHCHP electronic medical record (EMR), Medicaid data, and National Death Index (NDI) data as well as to collect supplemental housing data, health outcome data, and health cost and health utilization patterns. Using incidence rates or risk ratios and Cox proportional hazard models, we will compare these measures for clients during the 1-2 years prior to housing with the same outcomes at one, two, and three years of being housed. The study will provide critical new analysis as to whether Housing First is meeting its goals, thereby informing local and national stakeholders in how to move forward in preventing people from returning to homelessness and reducing health disparities among this vulnerable population.

Oral Biome Patterns as a Biomarker of Necrotizing Enterocolitis in Preterm Newborns

Principal Investigator: Richard Parad, MD, MPH, Brigham and Women's Hospital

Co-Investigator(s): Camilia Martin, MD, Beth Israel Deaconess Medical Center
Floyd Dewhirst, DDS, PhD, The Forsyth Institute

The pathophysiology of Necrotizing Enterocolitis (NEC) in premature newborns is poorly understood, but may be associated with colonization by an abnormal gut flora pattern. Preemies fed breast milk early have a significantly lower risk of developing NEC. Protection could be due to establishment of maternal flora over pathogenic ICU organisms. We neither know what organisms to look for, nor have the capability of culturing these organisms. The Forsythe Institute's Human Oral Microbiome Project has developed a human oral microarray that can detect nucleic acid fingerprints of approximately 300 of the 600 organisms found in the mouth, throat and lungs. The BWH NICU has a sample bank with tracheal aspirates from over 1200 intubated newborns born at <29 weeks gestational age. These samples contain traces of bacteria that likely reflect the oral and potentially enteral flora. Through a linked outcomes database, we propose to select infants with NEC and matched controls and compare tracheal aspirate flora patterns. In our hands, RNA and DNA can be extracted from these samples for microarray analysis. We thus propose a case-control study to address the question of whether tracheal (and thus presumably oral and enteric) flora differ between NEC and control cohorts, and if so whether specific organisms are prevalent. Identifying such biomarkers could both prove valuable in unraveling the pathophysiology of NEC and in identifying at risk patients for new preventive therapy strategies.

A Robot-Guided Positron-Probe System for Tumor Resection with Enhanced Accuracy at the Surgical Margins

Principal Investigator: Mi-Ae Park, PhD, Brigham and Women's Hospital
Alexandra Golby, MD, Brigham and Women's Hospital

Co-Investigator(s): Nobuhiko Hata, PhD, Brigham and Women's Hospital
Robert Howe, PhD, Harvard School of Engineering and Applied Sciences
Stephen Moore, PhD, Brigham and Women's Hospital

Maximal surgical excision of brain tumors confers a prognostic advantage. Intra-operative delineation of tumor tissue from critical brain tissue is difficult, because tumors resemble normal brain, and may infiltrate. Positron emission tomography (PET) with tumor-avid radiopharmaceuticals is useful for detecting tumors and for helping to define their locations for surgery, however, because of its poor spatial resolution, intra-operative PET is not being studied extensively. A plastic-scintillator-based positron probe can detect positrons originating within ~2 mm of the probe's tip. Since brain tumors are known to take up radiotracers in greater amounts than brain tissue, the use of a handheld probe capable of quantifying tracer concentration could allow surgeons to improve the intra-operative delineation of tumor margins. We propose to develop a reliable and robust robot-driven intra-operative system to assist surgeons in cleaning surgical margins of residual tumor tissue following bulk tumor resection. Our approach of integrating a robot and a positron probe within one intelligent system will (1) allow the probe to be held with no motion (shaking) immediately adjacent to the tissue, for a time interval computed to achieve reliable discrimination between tumor and non-tumor tissue, and (2) reduce radiation dose to the surgeon by increasing the distance between the patient and the surgeon guiding the probe. We currently have the positron detector probe with digital readout; in this cross-institution and multidisciplinary team project, we will integrate the probe with a surgeon-controlled robot positioning system, before seeking external funding to evaluate the system's performance in animal/or human surgical procedures.

Screening for Notch Inhibitors in Flies and Humans

Principal Investigator: Norbert Perrimon, PhD, Harvard Medical School

Co-Investigator(s): Jon Aster, PhD, Brigham and Women's Hospital

There is increasing interest in targeting the Notch pathway for purposes that pertain to human health and in particular cancer. One of the clearest examples of an oncogenic role for Notch1 is found in human T-cell acute lymphoblastic leukemia/lymphoma (T-ALL), in which gain-of-function mutations causing ligand-independent activation of Notch1 are found in over 50% of patients with aggressive cancer. Failed Phase I clinical trial of a Merck gamma-secretase inhibitor (GSI), MK-0752, opened for patients with refractory/relapsed T-ALL, highlighted two major hurdles that must be surmounted for Notch therapeutics to move forward: 1) There is a need to identify inhibitors with a better therapeutic index, or drug combinations that obviate the toxicity caused by conventional GSIs while maintaining or enhancing “on-tumor” effects”; and 2) There is a need to identify drugs that synergize with Notch pathway inhibitors to enhance “on-tumor” effects. To identify and characterize new Notch inhibitors, the Perrimon lab has developed a highly specific *in vivo* assay for Notch activity in the Drosophila gut that offers the opportunity to rapidly and cheaply screen small molecules and drug combinations. We propose to use the fly assay to perform a large-scale screen for small molecules that affect Notch signaling. Because the Aster lab has the capacity to test inhibitors and drug combinations in cell-based and murine leukemia assays, our collaboration has the potential to rapidly translate fly “hits” to pre-clinical trials in mice, or in the case of FDA-approved drugs, directly to human trials.

Toward a Neurobiological Understanding of Anhedonia in Major Depression: A Novel Raclopride-based Molecular Imaging Technique

Principal Investigator: Diego A. Pizzagalli, PhD, Faculty of Arts and Sciences, Harvard University

Co-Investigator(s): Nathaniel Alpert, PhD, Massachusetts General Hospital
Dan V. Iosifescu, MD, Massachusetts General Hospital

Depression is a major public health problem, both in terms of personal suffering and socioeconomic burden. Unfortunately, the causes and pathophysiology of major depressive disorder remain largely unknown. Moreover, progress in understanding the neurobiology of depression is hindered by the lack of objective measures of core depressive symptoms. Anhedonia, the loss of pleasure or lack of reactivity to pleasurable stimuli, has emerged as a promising endophenotype of depression due to its potential as a vulnerability marker for the disorder. The goals of the proposed work are: (1) to test the hypothesis that decreased phasic dopaminergic transmission within mesolimbic regions plays a key role in the pathophysiology of major depressive disorder and the emergence of anhedonia; and (2) to investigate phasic dopaminergic release in major depressive disorder using positron emission tomography (PET) techniques during a reinforcement learning task. These aims will be accomplished by bringing together a highly interdisciplinary research team involving three different departments (Psychology, Psychiatry, and Radiology), two different schools (Harvard Faculty of Arts and Sciences and Harvard Medical School), and expertise in clinical neuroscience, psychiatry, molecular imaging, and mathematical modeling. By combining molecular imaging, careful clinical characterization, and objective behavioral measure of core aspects of depression, the proposed study is expected to provide novel insights into pathways associated with increased vulnerability to this life-threatening and debilitating disease. If successful, the proposed research might provide novel targets for treatment strategies and disorder prevention, and critical pilot funding for larger, federally funded grant applications.

Development of a Point-of-Care Lab-on-a-chip Urine Antigen Detection Test for Active Tuberculosis

Principal Investigator: Nira Pollock, MD, PhD, Beth Israel Deaconess Medical Center

Co-Investigator(s): Antonio Campos-Neto, MD, PhD, The Forsyth Institute
Alexis Sauer-Budge, PhD, Fraunhofer USA

Improved methods to diagnose active tuberculosis(TB), and in particular sputum smear-negative or extra-pulmonary disease, are sorely needed. Worldwide, diagnosis of active TB relies primarily on sputum microscopy. However, sputum smears under field conditions detect only 40-60% of culture-proven cases of pulmonary TB, and sensitivity falls to as low as 20% in patients with HIV. We propose to develop a highly accurate, point-of-care urine antigen detection assay for diagnosis of active TB. Testing urine should in theory only detect M. tuberculosis(MTB) antigens generated by a large burden of actively dividing organisms and thus be specific for active (vs latent) TB. Moreover, this type of assay could provide a critical tool to monitor the effectiveness of treatment. Drs. Campos-Neto and Pollock, using mass spectrometry, have identified four MTB proteins present in the urine of patients with pulmonary TB. Preliminary data from ELISA and rapid immunochromatographic (RICH) test analysis shows that these antigens can indeed be detected in the urine of patients with active TB. However, conventional ELISAs cannot be done at point-of-care, and the detection limit of the RICH format (approximately 250 pg/ml) may be prohibitively high. In collaboration with Dr. Sauer-Budge, we propose to develop a completely automated and miniaturized, low-cost, lab-on-a-chip ELISA test (integrated disposable chip and instrument) for detection of our novel urinary TB antigens which 1) maintains or increases the sensitivity of conventional ELISA and 2) allows performance of ELISAs at point-of-care. This work has the potential to transform global TB control, particularly in resource-poor areas.

Using Pregnancy Outcomes to Predict and Prevent Cardiovascular Disease in Women

Principal Investigator: Janet Rich-Edwards, ScD, Brigham and Women's Hospital

Co-Investigator(s): Ananth Karumanchi, MD, Beth Israel Deaconess Medical Center

We propose a project that could kindle a paradigm shift in the prevention and detection of cardiovascular disease (CVD) in women. Surveys from Europe indicate that delivering a preterm or low birthweight infant doubles the risk that the mother will die from CVD in maturity. Determination of the mechanisms behind this striking observation is urgent, as 20% of US women will have a pregnancy complicated by hypertensive disorders, diabetes, or ending in preterm or low birthweight delivery. As African Americans have twice the risk of complicated pregnancies, the unexplored implications for their future health are even greater. To investigate these questions, a group of twenty basic and clinical researchers from Brigham and Women's, Beth Israel, and Children's Hospitals are collaborating to propose a large longitudinal cohort that would follow women longitudinally from pregnancy to detect emerging signs of CVD. To support proposal development, we need preliminary data from a U.S. population. The Nurses' Health Study II has collected data on pregnancy outcomes, lifestyle factors, and CVD risk factors and events for over 68,000 women, including several thousand African American women. This Catalyst proposal is to fund a new postdoctoral position for a fellow to analyse these data with Drs. Janet Rich-Edwards (BWH) and Ananth Karumanchi (BI). The findings would be important in their own right. The work would directly support the foundation of a longitudinal cohort to investigate how clinical characteristics of pregnancy can inform women's health care, generating novel methods to alter disease trajectories to prevent CVD in women.

Development of an Animal Model for Testing Cholera Vaccine Safety

Principal Investigator: Jennifer Ritchie, PhD, Brigham and Women's Hospital

Co-Investigator(s): Jonathan Kagan, PhD, Children's Hospital Boston
Tomas Kirchhausen, PhD, Harvard Medical School
John Mekalanos, PhD, Harvard Medical School
Matthew Waldor, PhD, MD, Brigham and Women's Hospital

Cholera, an acutely dehydrating secretory diarrheal disease caused by *Vibrio cholerae*, is endemic in many developing countries and remains a substantial, often under-reported, health burden worldwide. Many individuals in endemic regions do not have access to life-saving treatments for cholera; consequently, there is an urgent need for a safe, effective, and low-cost cholera vaccine. Oral live-attenuated *V. cholerae* vaccines have great potential to fulfill this need, since natural infection with *V. cholerae* is thought to bestow long-lasting protection against cholera. Current live-attenuated vaccine candidates consist of genetically modified *V. cholerae* strains that no longer produce cholera toxin, the causative agent of secretory diarrhea. However, administration of such ctx vaccines to human volunteers is associated with 'reactogenicity', defined as self-limiting, non-choleric 'fecal' diarrhea and stomach cramps. The causes of reactogenicity remain obscure, in part due to the lack of an animal model suitable for analysis of this problem. We have recently found that oro-gastric administration of *V. cholerae* to infant rabbits resulted in a cholera-like illness. Furthermore, administration of *V. cholerae* ctx mutants to infant rabbits results in transient fecal diarrhea resembling human reactogenic diarrhea. The two main aims of the proposed work are 1) to establish that infant rabbits are a good model of reactogenicity, using vaccine strains previously tested in human volunteers and 2) to determine the molecular basis of reactogenicity with the goal of designing safer vaccine candidates. This work will be an inter-disciplinary collaboration between microbiologists, cell biologists, and immunologists located at several Harvard-affiliated institutions.

Evaluation of Cardiac Disease Phenotypes *In Vitro* Using a Human Cardiomyocyte Cell Culture System Derived From Inducible Pluripotent Stem Cells

Principal Investigator: Anthony Rosenzweig, MD, Beth Israel Deaconess Medical Center

Co-Investigator(s): Chad Cowan, PhD, Massachusetts General Hospital
Laurence Daheron, PhD, Massachusetts General Hospital
Michael Rosenberg, MD, Beth Israel Deaconess Medical Center

Most adult human cardiovascular diseases are the result of complex genetic traits, whose manifestation is dependent on the intricate relationship between the individual's genome and the environment. Study of these traits in humans is difficult because even when affected patient material is available, study cannot often be propagated *in vitro*. To overcome this limitation, we describe in this protocol a plan to use inducible pluripotent stem (iPS) cell technology, refined in the Harvard Stem Cell Institute, to explore human cardiomyocyte biology of the complex genetic disease atrial fibrillation (AF) *in vitro*. AF is the most common arrhythmia, and despite being well-studied, has limited treatment options available, at least in part due to a lack of experimental models. In this study, we plan to obtain skin samples from patients with AF, as well as matched controls, isolate the fibroblasts, and reprogram the cells into iPS cells, which will provide an unlimited source of cells for future experimentation. Beginning with control samples for protocol optimization, we will differentiate the iPS cells into atrial cardiomyocytes and examine variability as well as gene expression for markers of differentiation. Then, in a case-control design, we will examine cellular electrophysiological properties and calcium handling properties in AF vs. control samples. We will also examine gene expression differences between the groups, and identify targets for future validation and treatment. This study is the first step towards our larger goal of establishing a human *in vitro* model of cardiac disease for biological exploration and patient-specific drug testing.

A Pilot Trial of Sonoelastography for Planning Tumor-targeted Prostate Biopsy

Principal Investigator: Anthony Samir, MD, Massachusetts General Hospital

Co-Investigator(s): Douglas Dahl, MD, Massachusetts General Hospital
Adam Feldman, MD, Massachusetts General Hospital
Scott McDougal, MD, Massachusetts General Hospital
Peter Mueller, MD, Massachusetts General Hospital
Shahin Tabatabei, MD, Massachusetts General Hospital
Chin-Lee Wu, MD, Massachusetts General Hospital

Prostate cancer is the most common malignancy in men in the United States. Current screening for prostate cancer consists of serum PSA measurement followed by transrectal ultrasound-guided prostate biopsy. Transrectal ultrasound is used to target the entire prostate gland, not the cancer itself, by performing between 6 and 12 non-targeted random biopsies of the prostate gland. The biopsies are non-targeted, as prostate cancer does not have a specific appearance on conventional ultrasound imaging. Unfortunately, non-targeted biopsy of the prostate fails to detect prostate cancer in up to 35% of cases. Consequently, many prostate cancers are diagnosed on repeat biopsy after a delay of months. Since the treatment and prognosis of prostate cancer is highly dependent on the extent to which the tumor is locally invasive, it is likely that this delay in diagnosis ultimately affects prognosis. Sonoelastography is a new diagnostic ultrasound technology that permits assessment of the stiffness of structures deep inside the prostate. Prostate cancer has been shown to be stiffer than normal prostatic tissue. Several studies have shown that sonoelastography increases the sensitivity of prostate biopsy for prostate cancer. We propose to undertake a pilot study in patients with known prostate cancer who are to undergo prostatectomy, in which we assess (1) whether biopsies planned with sonoelastography are more likely to intersect foci of tumor than random non-targeted prostate biopsies and (2) whether biopsies planned with sonoelastography will yield more representative tissue samples than non-targeted biopsies, using prostatectomy pathology as the gold standard.

Patient-Specific Particle Deposition Model to Predict Tobacco Smoke Injury in COPD

Principal Investigator: Raul San Jose Estepar, PhD, Brigham and Women's Hospital

Co-Investigator(s): Alejandro Diaz, MD, Brigham and Women's Hospital
Matthew Hancock, PhD, Brigham and Women's Hospital
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James Ross, MSc, Brigham and Women's Hospital
George Washko, MD, Brigham and Women's Hospital

Overall Hypothesis: Tracheobronchial tree morphology influences regional distribution of particle deposition and by doing so may mitigate inhalational injury in the lung. Overall Project Proposal: Using tobacco smoke as the exposure model, the regional distribution of computed tomographic measures of both emphysema and airway disease will be examined and correlated with the 3-Dimensional morphology of the tracheobronchial tree in current and former smokers. A validated airflow/particle deposition model will be applied to each subject's tracheobronchial tree to predict under simulated conditions of respiration the degree and distribution of particle deposition in the airways and distal parenchyma. The regional burden of airway and parenchymal disease will then be compared to the idealized particle deposition pattern obtained under simulated conditions. Our proposal is focused on personalizing this particle deposition model by generating 3-D airway tree reconstructions from high resolution CT scans. Such an effort may allow the prediction of inhalational injury patterns based upon an individual's airway morphology. By performing such an investigation, we may find that native airway structure may in part dictate which smoker will develop emphysema, chronic bronchitis, or both. Team Strengths: Our multidisciplinary team provides expertise in particle deposition, mathematical modeling, image analysis, computer programming, and clinical pulmonary medicine. Our team also has access to very detailed physiologic and radiographic data on a large cohort of current and former tobacco smokers. This latter cohort is provided by the Lung Tissue Research Consortium (LTRC) and the data is currently stored in Dr. Washko's lab in Brigham and Women's Hospital.

Development of an Innovative Test of Sustained Visual Function

Principal Investigator: Debra Schaumberg, ScD, OD, MPH, Brigham and Women's Hospital

Co-Investigator(s): Pedram Hamrah, MD, Massachusetts Eye and Ear Infirmary
Deborah Jacobs, MD, Beth Israel Deaconess Medical Center
Jeremy Wolfe, PhD, Brigham and Women's Hospital

Dry eye disease is a major public health problem affecting over 10 million Americans. It is characterized by chronic ocular surface pain and fluctuating vision impairment. There is a critical need for effective therapies for this disease, yet only one such therapy has actually made it through the regulatory process. One of the major limiting factors to making headway in the development of more effective pharmaceuticals for the treatment of dry eye disease has been the absence of a clinically meaningful measure of its impact on patients' vision. Standard measures of visual acuity have virtually no utility in dry eye disease, because they fail to capture the type of impairment seen in dry eye. The goal of this research project is to capitalize on the combined expertise of an interdisciplinary group of investigators to develop an innovative Sustained Visual Function Test (SVFT) that would accurately measure visual impairment in patients with dry eye disease. The SVFT will be based on a dynamic measurement of spatial vision, incorporating elements of spatial frequency and contrast, and sustainability of the response over time. The test will be designed to be relatively quick, easy to administer, and to successfully distinguish errors due to visual deterioration over time in dry eye subjects from errors due to lapses of attention or other reasons. Development of such a test will fill a critical need for the conduct of clinical trials in dry eye disease, and is of keen interest to researchers, clinicians, and the ophthalmic pharmaceutical industry.

Mechanistic Impact of the Novel *MTNR1B* Type 2 Diabetes Gene on Changes in Circadian, Metabolic and Sleep Physiology

Principal Investigator: Frank Scheer, PhD, Brigham and Women's Hospital
Richa Saxena, PhD, The Broad Institute

Co-Investigator(s): Orfeu Buxton, PhD, Brigham and Women's Hospital
Anne-Marie Chang, PhD, Brigham and Women's Hospital
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Steven Shea, PhD, Brigham and Women's Hospital
Dick Swaab, MD, PhD, Netherlands Institute for Neuroscience

A novel type 2 diabetes gene (*MTNR1B*) recently discovered by our group encodes the melatonin receptor 1B, and a common *MTNR1B* variant (rs10830963) raises fasting glucose and increases risk for type 2 diabetes. Since the hormone melatonin has primary effects on sleep and the circadian system, the goal of this proposal is to determine the mechanistic role of the circadian, sleep and metabolic systems on the effect of the *MTNR1B* variant on glycemic parameters. We have shown that disruption of sleep and the circadian system leads to adverse metabolic changes and increases diabetes risk. We thus hypothesize that the effect of rs10830963 on diabetes could be mediated via effects on sleep or circadian systems. We propose to genotype *MTNR1B* variants in ~650 participants in two workplace/field studies, ~250 participants in laboratory studies of circadian and sleep physiology, and ~40 individuals with available post-mortem studies of detailed melatonin receptor 1B expression in the suprachiasmatic nucleus, the master circadian pacemaker. Specifically, we will test for association of *MTNR1B* variants with circadian (neuroanatomy and physiology), sleep and metabolic variables. If *MTNR1B* increases risk of diabetes by influencing circadian physiology, we expect the genetic variants to have much stronger effects on these proximal phenotypes than on glycemic measures. Results of this study will inform the experimental design of prospective laboratory studies in a population pre-selected by genotype, contribute to a mechanistic understanding of diabetes that could lead to novel therapeutics, and highlight the importance of sleep and circadian parameters in diabetes clinical risk prediction.

Treating Children with Severe Burns Using Video Games

Principal Investigator: Jeffrey Schneider, MD, Spaulding Rehabilitation Hospital

Co-Investigator(s): Paolo Bonato, PhD, Spaulding Rehabilitation Hospital
Robert Sheridan, MD, Massachusetts General Hospital

Recent advances in topical and systemic antibiotics, early excision and grafting, and artificial skin substitutes have significantly improved survival rates after severe burns. With increased survival, clinicians face significant challenges in the design of rehabilitation interventions since severe burns lead to major functional impairments, including contractures and joint deformities, amputations and severe deconditioning. A complex multifactorial approach is implemented to design therapy interventions that control for stress exerted on the joints and speed and range of movement while maximizing the functional outcomes. The use of robotic and virtual reality technologies is very attractive in this context. Robotics provides a means to administer the “right amount” of therapy by progressively increasing resistance and range of motion as the subject progresses. Virtual reality gaming systems are able to engage subjects in the exercise routine in the form of video games. The “distraction” associated with virtual reality has been shown to be beneficial to patients undergoing rehabilitation following severe burns, but it has not been tied into an exercise routine. The objective of this project is to develop a platform that utilizes robotics and virtual reality to facilitate rehabilitation in children with severe burns. We intend to build and test a system to facilitate and monitor rehabilitation exercises and asses its usability in a small cohort of patients as a first step toward a systematic clinical evaluation of the potential impact of these technologies on burn rehabilitation.

A Low-Cost, Incentive-based Therapeutic Adherence Platform for Infectious Diseases Using Point-of-care Diagnostics and Mobile Telephony

Principal Investigator: Amit Srivastava, PhD, Children's Hospital Boston

Co-Investigator(s): Rachel Glennerster, PhD, Massachusetts Institute of Technology
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Christopher Hug, MD, PhD, Children's Hospital Boston
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Effective cures exist for several infectious diseases but patient adherence or compliance with therapy remains a serious problem. Patients often do not take medicines for the prescribed time or abandon therapy altogether; this exacerbates the overall disease burden and promotes the development of drug-resistant pathogens. Non-adherence presents a unique challenge in resource-constrained settings that are often beyond the reach of traditional health infrastructure. Behavioral economic studies show definitively that drug adherence is achievable via the dual approach of fail-safe monitoring and pertinent incentives. We propose to develop a novel and versatile therapeutic adherence platform for resource-constrained settings using anti-tuberculosis (TB) therapy as a model. TB remains a major public health concern more than 60 years after the first effective antibiotics were developed; a prime contributing factor globally is inconsistent patient adherence to the 6-9 month drug treatment regimen. Non-adherence contributes to morbidity, mortality and rise of multiply drug resistant (MDR) TB. Our platform allows for remote monitoring of patient compliance using encrypted, diagnostic paper microfluidic strips that detect metabolites of anti-TB drugs in the patient's urine. Adherence is reported to a central database via cell phone and is incentivized by a monetary rewards program. This new system is significantly less resource-intensive than the current standard: on-site, in-person monitoring of drug adherence, also known as Directly Observed Therapy Short Course (DOTS). Our multidisciplinary team, consisting of scientists, engineers, physicians and economists, envisages application of this adherence platform to other ailments with significant public health impact, such as insulin-dependent diabetes and smoking.

A Pilot Study of the Effectiveness of Point-of-purchase Menu Labeling and Choice Architecture in Promoting Healthier Food and Beverage Choices

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A major contributor to the obesity epidemic is a food environment that promotes excessive eating and energy-dense food and beverages. Mandatory menu labeling with nutritional information has been advocated by multiple public health groups, and despite strong opposition from the restaurant industry, legislation for menu labeling has been initiated in the U.S. Although recent laboratory studies in consumer psychology demonstrate that choice architecture (i.e., which foods are offered as the default) can affect food choice, the effectiveness of these interventions as well as menu labeling have not been tested in the real world. This Catalyst proposal is a pilot study of a 2-phase intervention to label all food and beverages and then to alter the choice architecture to increase healthy default items in the main cafeteria at Massachusetts General Hospital (MGH). The cafeteria, operated by the Department of Nutrition, serves over 6000 employees, visitors, and patients a day; 27% of daily revenues are purchased by employees using a card that tracks their purchases. This Catalyst will initiate a novel collaboration between a physician, 2 nutritionists, and a health economist from MGH with a consumer psychologist from Harvard Business School to conduct a real-world experiment of point-of-purchase food labeling and choice architecture. Cash register sales will be analyzed before and after the intervention phases. Data from the subset of employees using the cafeteria card will be analyzed to assess changes in individual purchasing behavior. Findings from this project will provide pilot data for conducting a multi-site randomized trial.

New Preoperative Factors Predict Resectability of Malignant Pleural Mesothelioma

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Malignant pleural mesothelioma (MPM) is a rare thoracic cancer that ultimately causes death by locoregional extension. Multimodality therapy that includes surgical extirpation of tumor by extrapleural pneumonectomy has yielded prolonged survival for a defined subset of patients. About 25% of patients, however, are deemed unresectable intraoperatively because of an inability to identify advanced local invasion of tumor preoperatively. Objective: To improve patient selection by identifying preoperative variables that are indicative of advanced local infiltration of MPM and thereby reduce the number of surgical candidates found to be unresectable at surgery. To validate these variables prospectively under an IRB-approved protocol. Aim 1: To identify variables in MPM patients that enable accurate prediction of resectability by cytoreductive surgery and develop a preoperative resectability index (PRI). We hypothesize that independent indicators of advanced locally invasive disease can be isolated. Aim 2: To determine the predictive accuracy of the factors identified in Aim 1 in a prospective clinical study. We hypothesize that the rate of resectability for patients brought to surgery will increase by using the PRI. Aim 3: To evaluate the survival effect in patients determined to be unresectable by PRI. We hypothesize that survival of unresectable patients will increase by deferring surgery as the primary treatment. Potential Impact: This study will improve patient selection, survival, and quality of life by deferring surgery in individuals deemed unresectable preoperatively. This novel approach to preoperative diagnosis has the potential to redefine the paradigm for determining eligibility for any locally invasive thoracic cancer.

Magnetic Resonance Spectroscopy Biomarkers in Duchenne Muscular Dystrophy

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Duchenne muscular dystrophy (DMD) is an incurable childhood disease and the most common pediatric muscular dystrophy, affecting 1 in every 3,500 male births. Boys with DMD suffer progressive loss of muscle strength and function: they are unable to walk by 13 years of age and die in their late teens or twenties. Disease progression is staged using strength and functional tests, such as dynamometry and timed tasks. These methods are limited in showing change over time and are influenced by patient effort or examiner variability. Furthermore, they do not provide insight of muscle physiology as the disease progresses or improves with therapy. Magnetic resonance spectroscopy (MRS) is an established non-invasive method to examine muscle physiology. There is preliminary evidence that muscle MRS of DMD patients shows abnormal concentrations of high-energy phosphates and other metabolites, which may serve as biomarkers for strength and functional status. We will perform cross-sectional studies using 31P- and 1H-MRS to measure energy metabolites, pH, indices of cellular turnover and adiposity in DMD patients compared to age- and BMI-matched healthy subjects. In DMD patients, we will correlate MRS data with results from standardized strength and functional tests. Our goal is to validate MRS as a safe and objective method to stage DMD without the use of ionizing radiation. This study will provide novel physiologic data and serve as the basis for non-invasive monitoring of emerging therapies for DMD. This proposal brings together investigators from three distinct specialties with unique strengths in MRS, DMD, and pediatric physical therapy.

Characterization of "KIMeter": A Biosensor for Early Detection of Kidney Injury

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Acute kidney injury (AKI) is a common medical condition with significant morbidity and mortality. Early detection of AKI before significant loss of kidney function would permit more timely diagnosis, prediction of injury severity, and safety assessment during drug development. Recently, kidney injury molecule-1 (Kim-1 in rats; KIM-1 in humans) was qualified by the US-FDA and EMEA as a highly sensitive and specific urinary biomarker to monitor drug-induced kidney injury in preclinical studies and on a case-by-case basis in clinical trials. The interventional therapy for AKI will ultimately depend on development of novel tools that allow rapid and continuous detection of biomarkers at the bedside. We propose to develop an optical resonance based biosensor (KIMeter: Kidney Injury Meter) that will facilitate sensitive, specific, rapid, economic, high throughput and 'online' detection of kidney injury. The first aim is to develop and evaluate the performance of KIMeter by conjugating anti Kim-1/KIM-1 monoclonal antibodies on silicon surface of the resonator. The change in the refractive index resulting from antigen-antibody binding will cause a corresponding change in the resonant frequency that will be detected by the photodiode. The second and third aims are to evaluate the use of KIMeter in preclinical safety assessment and as a bedside instrument in patient care by using urine samples from various forms of kidney injury in preclinical and clinical models of AKI in adult and pediatric population. Such a tool has the potential to transform safety assessment, environmental health screening and renal medicine towards effective and economic patient care.

Molecular Basis of Immunity Against Severe Malaria Mediated by the RTS,S/AS02 Vaccine

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Malaria causes 1-3 million deaths annually. The RTS,S candidate malaria vaccine contains sequences of the circumsporozoite protein (CSP) and has undergone Phase I/II trials with efficacy of 27-64%. Vaccine efficacy against severe disease was higher (~50%) than against infection and mild disease (~30%) in the Mozambique Phase IIb trial. Identifying parasite variants evading vaccine protection in severe cases could help elucidate the mechanism of protection against severe disease and improve vaccine immunogenicity. To protect an infected subject from contracting severe disease the vaccine may be selectively filtering pathogenic parasite variants with detectable signatures at the CSP locus. Alternatively the vaccine could be non-selectively limiting the multiplicity of parasite variants in an infection, thereby reducing the likelihood that a subject encounters parasites expressing antigens not previously encountered. We propose to study these hypotheses in a pilot study nested within the completed Mozambique trial in collaboration with investigators of the Malaria Genomic Diversity project, Harvard/Broad Malaria Initiative. In order to identify factors associated with vaccination failure we will compare vaccinees with infection versus those with severe disease with respect to: (1) parasite variants defined by signatures within the CSP locus, and (2) multiplicity of infection defined by diversity within the MSP locus. Differences between vaccinee groups will be contrasted to differences between non-vaccinee groups. At the conclusion of our study, we expect to propose a model to assess parasite evasion for studying malaria vaccines. Our results could support planning of confirmatory studies nested within the upcoming Phase III trials of the RTS,S/AS02.