Hearing loss is the most common sensory deficit in humans. One in 500 newborns has hearing loss and the frequency increases to one in 100 by school age. Congenital hearing loss can present as syndromic (accompanied by pathology in other organ systems), or nonsyndromic (where deafness is the only finding), with the latter accounting for approximately 70% of congenital hereditary deafness. Over 150 genetic loci have been discovered for nonsyndromic hearing loss, but causative genes have been identified for only about half. There is a critical need for clinical genomics applications to identify genetic and molecular etiologies of hearing loss. Through genomic sequencing of DNA from newborns who do not pass hearing screening, SEQaBOO will integrate high-throughput genomic approaches into routine newborn screening for hearing loss, to facilitate early and more precise diagnosis, more effective management, and better potential therapeutic interventions. We will analyze and assemble genomic data and, perform annual surveys of the cohort of children to ascertain general health, including speech and language development in addition to hearing status, and parental attitudes and implications of genomic sequencing in newborns.
Hearing loss is the most common sensory deficit in humans. One in 500 newborns has permanent hearing loss and that number increases to 1 in 100 children by school age. Early detection and intervention of hearing loss before the critical period of speech and language acquisition translate into improved social skills, academics, and quality of life. Universal newborn hearing screening was adopted in the U.S. since the 1990s. Massachusetts requires that all newborns be offered hearing screening prior to hospital discharge. Newborns who do not pass this initial screen are scheduled at approximately 1 month of age for a follow-up diagnostic hearing test. However, clinical diagnosis often does not distinguish among different types of hearing loss. SEQuABOO will investigate how genomic information may benefit and assist in providing care and management of newborns with hearing loss. Through genomic sequencing of DNA from newborns who do not pass hearing screening, we hope to provide the earliest possible diagnosis of any genetic cause of hearing loss, to guide optimal clinical management and avoid unnecessary diagnostic tests. In addition, through this project, we will ascertain the impact on the child's development through annual surveys regarding general health, hearing, and speech and language development.

**Clinical Implications (MUST be limited to 40 words and accessible to a lay audience) - please describe the clinical implications of your research.**

The SEQuABOO project is designed to elucidate possible genetic causes of hearing loss in newborns, to provide a better avenue for personalized medicine and more precise early diagnosis, better management, and more optimal targeted therapeutics for hearing loss.

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Research Fellow

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**Title**
Targeting Novel Regulatory Mechanisms of Phosphatidylcholine Metabolism in Lymphangioleiomyomatosis (LAM)

**Authors***
You Feng*, Taylor Kavanagh, Carmen Priolo

**PI***
Carmen Priolo

**Abstract Body (MUST be limited to 200 words, anything beyond 200 words will be truncated for print)**
LAM is a multi-system disorder caused by inactivating mutations in the Tuberous Sclerosis Complex (TSC) 1/2 gene. LAM consists of diffuse proliferation of smooth muscle actin-positive cells and cystic lung destruction. Extrapulmonary LAM includes renal angiomyolipomas. TSC2-deficiency leads to hyperactivation of mammalian Target of Rapamycin Complex 1 (mTORC1), stimulating cell growth and metabolism. More efficient therapies remain needed in LAM. We identified a potential role for autotaxin (ATX), a secreted lysophospholipase D, and CTP:phosphocholine cytidylyltransferase (CCT), a rate-limiting enzyme in phosphatidylcholine (PC) biosynthesis, in LAM therapy. PC is critical for organelle integrity/lipid droplet biogenesis. ATX converts lysophosphatidylcholine to lysophosphatidic acid (LPA), a bioactive lipid involved in tumor metastasis/angiogenesis. TSC2-deficient cells have enhanced choline incorporation into lipids and enhanced LPC secretion. We found that both ATX and CCT are upregulated in TSC2-deficient cells. GLPG1690, an ATX inhibitor in phase 2 clinical trial for pulmonary fibrosis, selectively suppresses the viability and migration of TSC2-deficient cells. ATX inhibition induces a significant decrease in Akt and ERK phosphorylation, CCT expression, and reprogramming of the TSC lipidome. Finally, CCT phosphorylation state changes upon mTORC1 inhibition, suggesting that CCT activity can be regulated both transcriptionally and post-translationally through mTORC1-dependent and independent mechanisms in TSC.

Lay Summary (MUST be limited to 200 words, anything beyond 200 words will be truncated for print). Please keep in mind - Discover Brigham is open to the public, this lay summary needs to be appropriate for lay audiences with NO scientific background. *

Lymphangioleiomyomatosis (LAM) is a rare disease of young women characterized by progressive destruction of the lung, shortness of breath, and renal and abdominal tumors. LAM leads to dependency on oxygen supplementation and lung transplant. Rapamycin, the FDA-approved treatment for LAM, decreases tumor size and stabilizes lung function in LAM patients; however, tumors regrow and lung function worsens when therapy is discontinued. More efficient therapeutic strategies remain needed in LAM. We have found that autotaxin is a secreted protein involved in the metabolism and survival mechanisms of TSC2-deficient cells derived from a LAM patient. Importantly, the drug targeting autotaxin (GLPG1690) that we are currently testing has been shown to be safe in clinical trials of patients with pulmonary fibrosis.

Clinical Implications (MUST be limited to 40 words and accessible to a lay audience) - please describe the clinical implications of your research.*

Clinical trials of mTORC1 inhibitor rapamycin showed partial response of tumors and stabilization of pulmonary function; however, tumor growth and lung function decline resumed when treatment was discontinued. Therapeutic regimens able to induce durable responses are urgently needed in LAM.
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If you selected 'other' please specify your research area:

Title*
A Focus Group Approach to Quality Improvement for Rheumatoid Arthritis Care

Authors*
Malka Forman; Cianna Leatherwood, MD; Maura Iversen, PT, DPT, SD, MPH, FNAP, FAPTA

PI*
Sonali Parekh Desai, MD, MPH

Abstract Body (MUST be limited to 200 words, anything beyond 200 words will be truncated for print)*
Background: Patient reported outcomes (PROs) are critical measures of disease severity and management in rheumatoid arthritis (RA) patients. Qualitative data from PRO focus groups can help identify key challenges to medication adherence in RA patients and guide optimization of management. Methods: BWH patients with RA were prospectively recruited and allocated into 3 focus groups and interviewed by a trained moderator. Patients’ responses were independently examined, categorized into themes, and codified by 3 reviewers. Common themes identified by all 3 reviewers were focused on for analysis. Results: 13 RA patients (age 28-73 yrs) were allocated into 3 focus groups. Following reviewer analysis of patients’ responses, 6 common themes that impacted the quality of RA care were identified: self-management strategies, clinical environment, healthcare delivery, patients’ attitudes towards medication, insurance-related issues, and lifestyle. Conclusions: Our preliminary findings demonstrate the feasibility and utility of employing focus groups to collect PROs for RA patients. Patient-reported barriers to medication adherence notably included patients’ attitudes towards medication and insurance-related issues. These preliminary results form the basis of a RA QA/QI program in medication adherence that includes patient education materials, implementation of patient support groups, and a series of provider-oriented learning sessions that review best practices.

Lay Summary (MUST be limited to 200 words, anything beyond 200 words will be truncated for print). Please keep in mind - Discover Brigham is open to the public, this lay summary needs to be appropriate for lay audiences with NO scientific background.

Rheumatoid arthritis (RA) is the most common autoimmune inflammatory arthritis in adults, affecting 1.3 million people in the U.S. RA may be characterized by inflammation and destruction of synovial joints, and often causes debilitating pain and inability to perform daily tasks. If left untreated, RA may cause disability and premature mortality. Over last two decades, the use of disease modifying anti-rheumatic drugs (DMARDs), specifically methotrexate and new biologic agents has dramatically improved RA management. Research suggests that early treatment of RA with DMARDs can significantly lower RA disease activity. Furthermore, high adherence to RA treatment has been shown to improve efficacy of therapy. However, adherence is difficult to achieve in patients with chronic inflammatory autoimmune illnesses due to the complexity of treatment regimens and the severity of medication side effects. This qualitative analysis was completed by the Division of Rheumatology at Brigham and Women’s Hospital. This study aims to describe patient perspectives about RA medication adherence and current attitudes towards their RA treatment regimens, and to optimize strategies for the management of RA to improve patient care.

Clinical Implications (MUST be limited to 40 words and accessible to a lay audience) - please describe the clinical implications of your research.

This study informed our efforts to enhance care for patients with RA. We began a quality improvement program in medication adherence that includes creation of patient education materials, patient support groups, and provider-oriented learning sessions that review best practices.

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First Name*  Katherine
Last Name*  Forsythe
Academic Degrees*  BA

BWH Department*  Information Systems
BWH Division (if applicable)  Clinical Quality and Analysis
BWH ID Number  100484296

Email Address*  kjforsythe@partners.org

BWH Title or HMS Rank (if relevant)*  Research Assistant

Twitter Handle (if applicable)

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Clinical Informatics

Title*  Incorporating the Indication into CPOE: Transforming Primary Care Medication Workflow

Authors*  Katherine Forsythe; Kevin Kron; Sara Myers; Aaron Nathan; Sam Karmiy; Isabella Newbury; Pamela Neri, MS; Alejandra Salazar, PharmD; Lynn Volk, MHS; Mary Amato, PharmD; Adam Wright, PhD; Enrique Seoane, PhD; Tewodros Eguale, PhD, MD; Sarah K.

PI*  Gordon Schiff, MD
Abstract Body (MUST be limited to 200 words, anything beyond 200 words will be truncated for print)*
Currently, medication orders lack information about the drug indication. Integrating indications could pave the way for a safer, more complete continuum of care for the patient and save time during prescribing and related tasks. The goal of this study is to use a user-centered design process to design and build a prototype indications-based CPOE system that is both safer and more efficient than current CPOE systems, which limit indications to after-the-fact additions and are viewed as cumbersome by prescribers. Six expert webinars were hosted to consult high-level stakeholders on system design considerations. To refine this list, we conducted 9 one-on-one contextual inquiry sessions with prescribers to observe prescribing activities and workflow, and 4 participatory design sessions to brainstorm design ideas directly with prescribers. We employed iterative usability testing of new screen designs and workflow modifications with prescribers to ensure their needs and priorities are met. From this we have developed a prototype CPOE which includes hundreds of features designed to improve usability and safety, many of which do so with medication indications information. Initial reactions to the prototype have been overwhelmingly positive and head-to-head testing of the prototype CPOE system is being conducted against two leading commercial vendors.

Lay Summary (MUST be limited to 200 words, anything beyond 200 words will be truncated for print). Please keep in mind - Discover Brigham is open to the public, this lay summary needs to be appropriate for lay audiences with NO scientific background.*
Currently, most electronic systems used for medical records do not incorporate indications (the reason for taking a drug) into prescriptions for medication. If indications were added to medications, it would help patients understand why they are taking their medications and would help pharmacists and doctors make sure the patient was receiving the correct medication for their problem. This goal of this study is to design an electronic system that incorporates indications into the prescribing process. To do this we hosted webinars to consult high-level stakeholders, like physicians and pharmacists, to get feedback on considerations for the design of this system. We then observed prescriber’s activities and workflow along with brainstorming ideas with them. Using this information, we designed a prototype that we then iteratively refined to ensure the needs and priorities of prescribers were met. From this, we created a prototype indications-based electronic system, which includes many features designed to improve safety and usability, many of which do so with medication indications information. Initial reactions have been overwhelmingly positive and we are conducting testing of our prototype system versus two leading electronic systems already being used in hospitals.

Clinical Implications (MUST be limited to 40 words and accessible to a lay audience) - please describe the clinical implications of your research.*
Our re-designed electronic system incorporates the reason for taking a drug into prescriptions for medications. It not only helps clinicians and pharmacists with efficient and knowledgeable prescribing, but also would increase patient medication safety and knowledge.

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Prospective role of plasma biomarker kidney injury molecule-1 in diagnosing and monitoring chronic kidney disease

Katherine J. Freedberg, Samuel A. P. Short, Isabel J. Hsu, Ragnar Palsson, Venkata S. Sabbisetti, Helmut Rennke, Isaac Stillman, Joseph V. Bonventre

Sushrut S. Waikar

Chronic Kidney Disease (CKD), an irreversible condition marked by progressive loss of kidney function, affects more than 10% of the U.S. population. Current tests for diagnosing and monitoring CKD, urinary albumin and serum creatinine, have limited diagnostic specificity and ability to predict progression to kidney failure. New biomarkers identified in animal and human studies, such as the type-1 transmembrane protein kidney injury molecule-1 (KIM-1), may improve the speed and accuracy of kidney diagnoses, as well as help assess changes in kidney function over time. We undertook this study to understand the relationship between KIM-1 and changes observed in kidney biopsy specimens, which are the gold standards for diagnosis. We collected plasma from 522 patients at the time of native kidney biopsy and measured plasma KIM-1 levels using Luminex-based assays. Histopathological diagnoses were adjudicated by two pathologists. Associations between biomarker expression and histopathological lesions were tested using Spearman correlations and multivariable linear regressions. KIM-1 levels were inversely correlated with estimated glomerular filtration rate and directly correlated with proteinuria. KIM-1 was also elevated in patients whose kidney biopsies showed greater degrees of acute tubular injury and tubulointerstitial fibrosis. Plasma KIM-1 may serve as a non-invasive indicator of acute and chronic tubular injury.
Chronic Kidney Disease (CKD), a disease marked by a loss of kidney function, is a widespread condition affecting more than 10% of the U.S. population. The best way to make an accurate diagnosis of CKD is using a kidney biopsy. However, kidney biopsies are invasive procedures that can cause bleeding complications. We conducted a study to determine if blood and urine tests taken at the time of a kidney biopsy could predict the results of the kidney biopsy. To do this, we collected blood and urine samples before patients underwent biopsies and measured a number of new markers in the samples. One of these markers is named kidney injury molecule-1, which was identified in animal studies as a promising test for injury to the kidney. We correlated the levels of kidney injury molecule-1 with the results of the kidney biopsies in over 522 patients. We found that KIM-1 can potentially identify certain forms of kidney disease without the need for a kidney biopsy. In the future, we will test KIM-1 and other markers in our patients to see if they can ultimately improve the care of patients with kidney disease.

Clinical Implications (MUST be limited to 40 words and accessible to a lay audience) - please describe the clinical implications of your research.*

By developing new tests to more quickly and accurately diagnose and track kidney impairment, we hope to give doctors more effective tools to recognize and treat kidney disease. Eventually, these tests may decrease the reliance on invasive biopsies.
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If you selected 'other' please specify your research area:

Title*
A Checklist to Prepare Patients for Safe Discharge from the Hospital: Development and Pilot Results

Authors*
Fuller TE, Schnipper JL, Dalal AK

PI* Dalal AK

Abstract Body (MUST be limited to 200 words, anything beyond 200 words will be truncated for print)*
Motivation: The discharge process can be chaotic, and miscommunications can lead to adverse events and potentially avoidable hospital readmissions. Our objective was to refine and pilot a checklist used by patients and caregivers to self-assess preparedness for discharge. Methods: We iteratively refined a previously developed pre-discharge checklist with patients, patient advocates, clinicians, and subject matter experts for content validity and comprehension. During a 2-week pilot in the summer of 2017, we administered the checklist to general medicine patients and/or family caregivers 24-48 hours prior to their expected discharge date. Results: The final checklist was comprised of 16 statements across 4 domains (“My Understanding”; “My Medications”; “My Self Care Management”; “My Follow-up Care”), and one open-ended question. During the pilot, 17 checklists were administered and completed. 2.6 +/- 2.1 barriers to discharge were identified per patient, most commonly relating to medications and follow-up care. Conclusions/Implications: Most patients who completed a checklist during hospitalization identified concerns related to their discharge preparedness that, if addressed by the clinical team, could improve safety during transitions. Future studies should evaluate interventions that systematically administer checklists to patients, and that communicate identified concerns to the clinical team prior to discharge.

Lay Summary (MUST be limited to 200 words, anything beyond 200 words will be truncated for print). Please keep in mind - Discover Brigham is open to the public, this lay summary needs to be appropriate for lay audiences with NO scientific background. *

The discharge process can be challenging for patients and family members. Often problems come up just as patients are leaving, and sorting those issues out make the discharge process more frustrating and lengthy than it needs to be. We wanted to create a way for patients and family members to know what questions to ask as they plan for discharge. Working with doctors, nurses, patients, and family members, we created a pre-discharge checklist to help patients self-assess discharge preparedness. The goal of administering the checklist is to identify potential concerns patients may have about their understanding of the plan, medications, self-care instructions, and follow-up. We wanted to make sure people thought about their discharge plan early in their hospitalization, so we gave the checklist to 17 people at Brigham and Women’s Hospital a day or two before their actual discharge date. We found out that people often are unsure about many aspects of the discharge plan, mainly related to medications and follow-up, and often have questions that they want to discuss with their care team. We hope to give the checklist to many more patients, in the hopes of improving the discharge process for all.

Clinical Implications (MUST be limited to 40 words and accessible to a lay audience) - please describe the clinical implications of your research.*

This pilot research shows that discharge barriers exist for many patients. More research is needed to determine how best to administer the checklist, and how communicate concerns about discharge to the care team.

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- Women's Health & Gender Biology

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Title*
Modeling Acute Kidney Injury with Transition to Fibrosis in vitro using Nephron Organoids

Authors*
Edgar Garcia, Navin Gupta, Tomoya Miyoshi, Koichiro Susa, Sabbisetti Venkata, Joseph Bonventre, Ryuji Morizane

PI*
Ryuji Morizane

Abstract Body (MUST be limited to 200 words, anything beyond 200 words will be truncated for print)*
Fibrosis is a hallmark of chronic kidney disease resulting from failure to regenerate tubules after repeated injury. Traditional human cell culture models lack the diverse cell types necessary for fibrosis, while traditional animal models lack the heterogeneity of human solute transporters. Human pluripotent stem cell-derived nephron organoids enable the study of multi-compartment interactions of kidney tissue necessary for the study of fibrosis in vitro. Here, we examine the response of nephron organoids to repetitive treatment with cisplatin, an anti-cancer drug which often causes nephrotoxicity. Immunohistochemistry revealed nephron organoids are populated by PDGFR⁺ pericytes and fibroblasts, the origins of myofibroblasts, in a way that parallels human nephrectomy samples. Repeated cisplatin treatment induced profibrotic phenotypes including dedifferentiation and G2/M cell cycle arrest in LTL⁺ proximal tubules. Further cisplatin treatment showed myofibroblast activation, as well as collagen I and fibronectin accumulation in the interstitial space as characteristic of kidney fibrosis. Treatment with a fibronectin assembly inhibitor demonstrated inhibition of fibrosis.

The above experiments highlight the ability of nephron organoids to model fibrosis in vitro. Additionally, modification of the fibrotic state through drug treatments underscore the potential of this novel platform for mass drug screens in a way that is superior to traditional models.

Lay Summary (MUST be limited to 200 words, anything beyond 200 words will be truncated for print). Please keep in mind - Discover Brigham is open to the public, this lay summary needs to be appropriate for lay audiences with NO scientific background.

Kidney fibrosis is the build up of scar tissue that results from efforts to repair kidney tubules after injury. It is a hallmark of chronic kidney disease, an illness affecting approximately 14 percent of adult populations in the world. Modeling kidney fibrosis in a dish would enable drug screening to determine the efficacy of various drugs in alleviating fibrosis. Current efforts to model fibrosis are limited by both time and cost, but are more broadly limited by the inability to replicate human kidney pathophysiology. The creation of kidney tissue from human stem cells thus pose a solution to these problems. However, previous experiments have not fully shown whether kidney tissue produced from stem cells is capable of modeling fibrosis. To determine this, we treated our kidney tissue with a drug that is often used for cancer therapies, cisplatin. After treatment, we found an increase in both the cell population that produce scar tissue, as well as an increase in the scar tissue itself. Concurrent treatment of cisplatin with a new drug showed inhibition of fibrosis. Here, we produced a state resembling kidney fibrosis in a dish that can be used to explore new treatment options for this pathology.

Clinical Implications (MUST be limited to 40 words and accessible to a lay audience) - please describe the clinical implications of your research.*

We show evidence that human kidney tissue derived from human pluripotent stem cells can be used to model fibrosis in vitro. This novel model can then be used to both explore the mechanism of the disorder, and enhance drug development.

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Title*
A Genome Wide Association Study (GWAS) Identifies a Novel Susceptibility Locus Related to Risk for Sporadic Lymphangioleiomyomatosis

Authors*
Krinio Giannikou1*, Sungho Won2,3,4*, Wonji Kim2, John R. Dreier1, Xintao Qiu5, Magdalena Tyburczy1, Edwin K Silverman1,6, Elżbieta Radzikowska7, Elizabeth P. Henske1, Gary Hunninghake1, Prakash Rao5, Henry Long5, Joel Moss8, Miquel Pujana9, David J. Kwiatkowski

PI*
David J. Kwiatkowski
Abstract Body (MUST be limited to 200 words, anything beyond 200 words will be truncated for print)*

Lymphangioleiomyomatosis (LAM) is a rare aggressive low-grade neoplasm affecting almost exclusively women. LAM can either be associated with Tuberous Sclerosis Complex or be sporadic and is due to TSC2/TSC1 alterations. We hypothesized that DNA sequence variants beyond TSC2/TSC1 are associated with susceptibility/risk for LAM development, and performed a GWAS. DNA from saliva from 479 sporadic adult female S-LAM patients of European ancestry and 1261 matched healthy female control subjects from the COPDGene cohort was genotyped (Illumina). Standard quality controls were employed to exclude outliers, and 550,923 SNPs were analyzed. Conditional logistic regression for matched cases/controls was done. Two intergenic SNPs met genome-wide significance, rs4544201 (P=2.8×10^{-9}) and rs2006950 (P=2.9×10^{-8}), both in the same LD block on chr15q. These findings were replicated with an independent set of 220 S-LAM cases and 1214 male controls, with P=2.1×10^{-5} and 1.5×10^{-6}, respectively. Another SNP within this LD block, rs4561414, has a tissue-specific eQTL relationship with NR2F2 expression in thyroid, P=3.7×10^{-6}; a key transcription factor in neural crest, candidate cell of origin for LAM. NR2F2 expression assessed by RNA-seq was higher in LAM/angiomyolipoma (a LAM-related tumor) than in any TCGA cancer type, and was identified as a super-enhancer in H3K27ac ChIP-seq data. Functional assessment of NR2F2 is in progress.

Lay Summary (MUST be limited to 200 words, anything beyond 200 words will be truncated for print). Please keep in mind - Discover Brigham is open to the public, this lay summary needs to be appropriate for lay audiences with NO scientific background.*

Lymphangioleiomyomatosis (LAM) is a rare lung neoplastic disorder that causes difficulty breathing and can be fatal. It is commonly seen in individuals with a genetic disease Tuberous Sclerosis Complex (TSC), but also occurs in other women, sporadic LAM (S-LAM). Current understanding of S-LAM disease etiology is limited. We assumed that DNA alterations across entire genome may be associated with S-LAM. Genome-wide association studies (GWAS) are studies usually conducted with case-controls that enable to identify such genetic variants that contribute to better understanding of disease and be candidate diagnostic/prognostic markers as well as drug targets. We performed a GWAS and compared the genotype frequencies between 479 female adult S-LAM cases of European ancestry and 1261 female healthy volunteers. We used standard GWAS statistical analysis approaches and genetic alterations whose frequencies were significantly different between cases and matched healthy controls were considered as candidate genetic risk factor for S-LAM. We identified a novel susceptibility locus nearby NR2F2 gene in chromosome 15, related to risk for S-LAM; this data was significantly replicated in an independent set of 220 S-LAM
cases and 1214 controls. The mechanism related to these genetic findings and NR2F2 role in LAM disease development is further investigated.

Clinical Implications (MUST be limited to 40 words and accessible to a lay audience) - please describe the clinical implications of your research.*

Through genetic analysis, we identified a new gene involved in LAM disease development, NR2F2. We are currently focusing on understanding its role in greater detail, and figuring out how we can treat LAM based on this new information.

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First Name*  |  Last Name*  |  Academic Degrees*  
Leah          |  Gillon    |  B.S. in Biological Anthropology  

BWH Department*  |  BWH Division (if applicable)  |  BWH ID Number  
Cardiovascular  |                        |                        

Email Address*  |  BWH Title or HMS Rank (if relevant)*  
lgillon@bwh.harvard.edu  |  Researcher  

Twitter Handle (if applicable)  

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- Women's Health & Gender Biology  

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Title*  
Sudomotor Function Assessment in Nondiabetic Patients Presenting to a Cardiovascular Clinic  

Authors*  
Leah Gillon  

PI*  
Calum MacRae  

Abstract Body (MUST be limited to 200 words, anything beyond 200 words will be truncated for print)*  
We evaluated 310 consecutive nondiabetic patients presenting to a cardiovascular clinic with a novel sudomotor function assessment—Sudoscan—to assess sweat
gland innervation and peripheral nerve function. Using the medical record, we evaluated the utility of peripheral nerve function to rapidly assess cardiovascular health and disease. We found a correlation between electrochemical skin conductance (ESC) of the palms and soles and various components of cardiovascular condition. We observed lower ESC in patients positive for several cardiovascular risk factors (CVRFs) than their respective CVRFs-negative counterparts. There was also a direct correlation between CVRF score and ESC. We also observed lower ESC in patients positive for coronary artery disease (CAD) than their CAD-negative counterparts. While this relationship is known in diabetic patients where clinical autonomic neuropathy is evident, we observed a strong correlation even in a non-diabetic population. We hypothesize that as a result of autonomic nervous system dysfunction, measuring sweat gland innervation (via ESC) can serve as a surrogate for evaluating cardiovascular condition.

**Lay Summary (MUST be limited to 200 words, anything beyond 200 words will be truncated for print). Please keep in mind - Discover Brigham is open to the public, this lay summary needs to be appropriate for lay audiences with NO scientific background.**

Cardiovascular disease (CVD) is a leading cause of death in developed and developing nations. Due the invasive, expensive and time-consuming nature of most cardiovascular assessments, establishing a non-invasive and rapid test to assess cardiovascular condition would facilitate better methods of early diagnoses and intervention, thus decreasing the overall burden of CVD. To this end, we explored the possibility that a patented, FDA-approved device used to non-invasively, rapidly evaluate the integrity of the sweat response could innovatively inform physicians about their patients’ cardiovascular condition, on the basis that normal functioning of both the heart and the sweat glands are both controlled by the same system: the autonomic nervous system. We found patients’ sweat responses were related to their risk of cardiovascular morbidity and mortality. Decreased sweat gland function was observed in patients with the following variables known to correlate with increased risk of heart attack or stroke: high cholesterol, being a current or former smoker, having renal disease, being older than fifty, and having coronary artery disease.

**Clinical Implications (MUST be limited to 40 words and accessible to a lay audience) - please describe the clinical implications of your research.**

We examine the efficacy of a new, easily operated, bedside device to assess cardiovascular risk via sudomotor function testing. That cardiovascular health can be evaluated non-invasively by very simple measurements could assist earlier diagnoses and intervention in myriad clinical settings.

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If you selected 'other' please specify your research area:

Title*
PORTABLE DEVICE FOR INTERMITTENT SOCKET COMPRESSION

Authors*

PI*
C. Keith Ozaki, M.D. and Louis Nguyen, M.D.
Patients with dysvascular amputations, or amputations resulting from poor blood circulation, frequently experience a progression of the underlying disease that can result in additional, higher-level amputations. Intermittent compression (IC) therapy increases blood flow to the extremities and increases limb salvage rates, yet patient compliance has been shown to strongly correlate to its effectiveness (Van Bemmelen, 2001). The lack of portability is thought to be a primary factor negatively impacting compliance. Therefore, a portable device (P-DISC) was developed that can be embedded into a prosthetic socket and is capable of mimicking the peak pressures and timing of current intermittent compression therapy devices. This approach would allow the patient to receive IC therapy whenever the socket is donned. Data generated from three subjects show overall positive responses to therapy from the IC device, quantified by an increase in tissue oxygen saturation (%StO2). Our current hypothesis is that the pre-compression of the limb produced by the prosthetic socket hinders the effectiveness of the IC therapy when compared to IC therapy in non-prosthetic applications. We are continuing to explore the cause of the baseline pressure on the effectiveness of IC therapy.

Ulceration is the single most common precursor to lower limb amputation and has been identified as a component in 85% of cases. If the circulatory system cannot provide oxygen and nutrients to meet the metabolic demands of the skin-related tissues, ulcers may develop from inadequate oxygen delivery after a below-knee amputation. Eventually these ulcers are more likely to lead to re-amputation of the limb. Rapid intermittent compression (IC) therapy has been demonstrated to increase blood flow to the extremities, increase limb savable rates, relieve rest pain, and limit tissue damage. However, none are truly portable due to the size and power consumption of pumps that are used to create the pressure applied to the limb. This study tests a new investigational prosthetic socket developed by Liberating Technologies, Inc. (LTI) called Portable Device for Intra-Socket Compression (P-DISC). The socket is equipped with a portable device to provide IC therapy to offer benefits to people with abnormal vascular function in amputation. Data generated from testing the P-DISC device on three patients suggests the P-DISC device which mimics current IC devices was successfully created but the clinical benefit of the applying IC therapy within a prosthetic socket must be investigated further.

If shown to be effective, portable IC therapy device could be used to reduce re-amputation rates in those individuals with poor tissue perfusion (blood flow) and the associated elevated risk of further amputation.
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- [ ] Regenerative Medicine
- [ ] Women's Health & Gender Biology
- [x] Bioinformatician

If you selected 'other' please specify your research area:

Title*
Growing Genomic Networks from the Desktop to the Cloud with R and Bioconductor

Authors*
Shweta Gopaulakrishnan, BJ Stubbs, Peter Castaldi, John Platig, Vincent Carey

PI*
Vincent Carey

Abstract Body (MUST be limited to 200 words, anything beyond 200 words will be truncated for print)*
Fulfillment of the promise of genomic personalized medicine requires detailed interpretation of human DNA sequence variation. Effects of variants are context-dependent, and overall interpretation involves networks of annotations assembled from thousands of genome-scale experiments that evaluate protein-DNA binding, DNA accessibility, and effects of variants on expression of nearby or remote genes. Many of these relationships vary from organ to organ, so that comprehensive cataloging of genomic causes of disease will ultimately involve very massive volumes of annotation. We describe a preliminary attack on synthesizing available annotation to understand mechanisms of lung disease, using R/Bioconductor interfaces to high-resolution annotation assembled in MongoDB, Apache Drill, and Google BigQuery. These platforms were benchmarked to get a broader understanding of local versus cloud computing storage needs, monetary costs, and performance benefits, revealing that for medium sized datasets, local computing works best. TxRegQuery is an R package we developed that utilizes the R packages mongolite, GenomicRanges, and bigrquery to provide users with specialized tools for information access, retrieval from both MongoDB/Drill and BigQuery backends. TxRegQuery makes it possible to extract data in the form of GRanges objects, which can be filtered and intersected to create node-edge lists used in the formulation of regulatory networks.

Lay Summary (MUST be limited to 200 words, anything beyond 200 words will be truncated for print). Please keep in mind - Discover Brigham is open to the public, this lay summary needs to be appropriate for lay audiences with NO scientific background. *

New approaches to treating disease make use of detailed studies of our genes. Recent research has shown that it is not enough to know how DNA codes our genes -- we need to know how one person’s DNA differs from another’s. Each difference that is found can lead to changes in how our cells change over time, recover from illness, or respond to medicines. We have built a software tool, TxRegQuery, to be used by doctors who are working to discover new medicines. This tool helps them to interpret DNA, along with other individualized characteristics, so that diseases are treated more effectively.

Clinical Implications (MUST be limited to 40 words and accessible to a lay audience) - please describe the clinical implications of your research.*

Our software tool, TxRegQuery, can be used by doctors who are working to discover new medicines. This tool helps them to interpret DNA, along with other individualized characteristics, so that diseases are treated more effectively.

*  
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First Name*  
Korneel

Last Name*  
Grauwet

Academic Degrees*  
Dr. - Ir. - Ing.

BWH Department*  
Neurosurgery

BWH Division (if applicable)  

BWH ID Number  
100448304

Email Address*  
kgrauwet@bwh.harvard.edu

BWH Title or HMS Rank (if relevant)*  
PhD

Twitter Handle (if applicable)

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If you selected 'other' please specify your research area:

Title*  
Engineering the next generation of oncolytic HSV-1 vectors in the treatment of glioblastoma brain tumor

Authors*  

PI*  
Prof. EA Chiocca

Abstract Body (MUST be limited to 200 words, anything beyond 200 words will be truncated for print)*
Glioblastoma multiforme (GBM) is an aggressive brain tumor with a median survival of 15 months. Treatment with therapeutic oncolytic viruses (OV) have shown promise, although hurdles have been identified. The innate immune system, Natural Killer (NK) cells in particular, has been identified to prematurely eliminate HSV-1-based OVs before reaching its full therapeutic potential (Alvarez-Breckenridge et al., 2012). Therefore, we aimed to modify current HSV-1-based OV rQNestin34.5, awaiting Phase I clinical trials for recurrent GBM, to overcome this hurdle by inserting NK cell-evasive genes in the viral genome. In this study, we have inserted viral NK cell-evasive genes pseudorabies virus (PRV) gD or human cytomegalovirus (HCMV) UL141 driven by a CMV promoter into the viral genome of rQNestin34.5, to be expressed on or secreted by rQNestin34.5-infected cells. These NK cell-evasive genes have been identified to reduce NK cell-mediated recognition and killing by avoiding the activating NK cell receptor DNAM-1 through reduction of its ligands, CD112 and CD155, on the infected cell surface. We identified that the novel rQNestin34.5 expressing PRV gD or HCMV UL141 gained the ability to remove CD112 or CD155 from the cell surface, increasing its therapeutic efficacy in mouse models engrafted with patient-derived GBM stem cells.

Lay Summary (MUST be limited to 200 words, anything beyond 200 words will be truncated for print). Please keep in mind - Discover Brigham is open to the public, this lay summary needs to be appropriate for lay audiences with NO scientific background. *

Glioblastoma multiforme (GBM) is an aggressive brain tumor with a median survival of 15 months, resistant to current treatments. Promising prospects have been realized with oncolytic viruses (OVs). These viruses selectively infect, replicate in and lyse tumor cells. As OVs replicate within the tumor, they can efficiently spread throughout the tumor. Our group has identified the patients’ immune system to actively and effectively target HSV-1-based OVs (HSV-1: herpes simplex-1; cold sores) and remove the OV before it reached its optimal therapeutic potential, preventing its replication and spreading. Natural Killer (NK) cells, a branch of the innate immunity and first line of defense against invading pathogens, were found to be responsible for prematurely eliminating the OV from the tumor. To resolve this hurdle, we adapted rQNestin34.5, OV awaiting Phase I clinical trials in patients for recurrent GBM, to express genes from other viruses identified to avoid elimination by NK cells. Expression of NK cell-evasive genes pseudorabies virus (PRV) gD and human cytomegalovirus UL141 during infection helps the OV to hide from the patients’ immune system, preventing premature elimination of the OV by the patients’ NK cells and resulting in an increased therapeutic efficacy in mouse models engrafted with patient-derived GBM cells.

Clinical Implications (MUST be limited to 40 words and accessible to a lay audience) - please describe the clinical implications of your research.*

This research leads to the development of the next generation of HSV-1-based oncolytic viruses with increased therapeutic potency and can be combined with existing transgene-based strategies, such as T-VEC (first FDA approved OV in the treatment of melanoma).

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If you selected 'other' please specify your research area:

Title*
Sex differences in coronary microvascular dysfunction in individuals with diabetes

Authors*
Haas, AV, Rao AD, Garg R, Di Carli MF

PI*
Adler GK

Abstract Body (MUST be limited to 200 words, anything beyond 200 words will be truncated for print)*
Females have increased coronary microvascular dysfunction compared to males. This study sought to determine if this sex disparity is also present among individuals with type 2 diabetes. We performed a post-hoc analysis of baseline
Data from a previously published study showing that mineralocorticoid receptor blockade has beneficial effects on microvascular dysfunction in patients with type 2 diabetes. The current study included males (n=50) and females (n=28) without clinical evidence of obstructive coronary artery disease. Decreased coronary flow reserve (CFR), the ratio of adenosine-stimulated to resting myocardial blood flow (MBF) assessed by cardiac positron emission tomography reflects microvascular dysfunction and is a well-established intermediate marker of cardiovascular disease. In multivariate analysis, we found that females have significantly lower CFR (2.491±0.800) compared to males (2.933±0.705), p-value 0.018. Additionally, females have increased resting MBF (p-value 0.000). Also, at baseline, females have larger increases in aldosterone in response to infused angiotensin-II infusion than do men (p-value 0.018). These findings suggest that among individuals with type 2 diabetes, females have disproportional evidence of myocardial perfusion dysfunction. One mechanism may be dysregulated aldosterone production. Further research is needed to identify additional mechanisms contributing to these gender differences.

Lay Summary (MUST be limited to 200 words, anything beyond 200 words will be truncated for print). Please keep in mind - Discover Brigham is open to the public, this lay summary needs to be appropriate for lay audiences with NO scientific background. *

Heart disease is the leading cause of death in women. Impaired functioning of small blood vessels in the heart, termed coronary microvascular dysfunction, is associated with increased death from heart disease. Some studies suggest women have more coronary microvascular dysfunction than do men. We sought to determine if this sex difference is present in individuals with diabetes. We studied 50 men and 28 women with type 2 diabetes but without clinical evidence of heart disease. We determined coronary flow reserve (CFR), a measure of coronary microvascular function, using cardiac positron emission tomography. Lower CFR predicts cardiovascular death. We found that women have lower CFR when compared to men. Our previous study showed that blocking the effects of aldosterone improves CFR in individuals with diabetes. Therefore, we also examined aldosterone production. Women produce more aldosterone than men. These findings show that among individuals with type 2 diabetes, women have more coronary microvascular dysfunction compared to men. One mechanism for this dysfunction may be excess aldosterone production in women. Further research is needed to identify treatments to improve coronary microvascular dysfunction in women. This is critically important as there are no guidelines for treating coronary microvascular dysfunction.

Clinical Implications (MUST be limited to 40 words and accessible to a lay audience) - please describe the clinical implications of your research.*

These findings show that among individuals with type 2 diabetes, women have more coronary microvascular dysfunction compared to men. This is critically important as there are no guidelines for treating coronary microvascular dysfunction.

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If you selected 'other' please specify your research area:

Title*

Genetic variation at the coronary artery disease risk locus GUCY1A3 modifies cardiovascular disease prevention effects of aspirin

Authors*

Kathryn Hall, Thorsten Kessler, Julie E. Buring, Dani Passow, Howard Sesso, Robert Zee, Paul M Ridker, Heribert Schunkert, Daniel I. Chasman

PI*

Kathryn Hall
Background There is variability in response to aspirin therapy for primary prevention of cardiovascular disease (CVD). An allele of GUCY1A3 modifies platelet function and increases CVD risk. Here we investigated whether homozygous carriers of the risk allele (63% of a European population) benefit from aspirin in primary prevention. Methods The GUCY1A3 variant rs7692387 was examined post hoc in two long-term, randomized placebo-controlled trials of aspirin in primary CVD prevention: the Women’s Genome Health Study (WGHS, N=23,294), a large subset of the Women’s Health Study, and a myocardial infarction (MI, N=588) and stroke (n=259) case-control set from the Physician’s Health Study I (PHSI, N=22,071). Risk of bleeding was evaluated in the WGHS. Results In the WGHS, the GUCY1A3 risk-allele was associated with significantly higher rates of CVD among women randomized to placebo (Hazard Ratio (HR) 1.38 [(95%CI) 1.08-1.78], P=0.01). With randomized aspirin treatment, this effect was reversed (HR[95%CI]=0.90[0.72-1.11], P=0.31; Pinteraction=0.01). The aspirin effect trended toward lower rates of CVD among homozygotes of the risk-allele (HR[95%CI]=0.83 [0.67-1.04], P=0.08) but higher rates among heterozygotes (HR[95%CI]=1.39 [1.01-1.90], P=0.04). In PHSI, there were concordant trends of rs7692387 with randomized aspirin allocation for CVD (Pinteraction=0.06) that were significant for MI (Pinteraction =0.02) but not stroke (Pinteraction =0.23). Meta-analysis of the WGHS and PHSI revealed a 23% reduction of CVD (OR[95%CI]=0.77[0.62-0.95], P=0.02) among homozygotes of rs7692387 randomized to aspirin. Differential bleeding effects of aspirin according to GUCY1A3 genotype were modest. Conclusions Individuals homozygous for the GUCY1A3 rs7692387 risk allele benefited from aspirin treatment whereas the other genotypes did not. Knowledge of GUCY1A3 genotype may facilitate precision of aspirin treatment in primary prevention of CVD.

Lay Summary (MUST be limited to 200 words, anything beyond 200 words will be truncated for print). Please keep in mind - Discover Brigham is open to the public, this lay summary needs to be appropriate for lay audiences with NO scientific background. *

While the efficacy of aspirin is well established for individuals who have a history of myocardial infarction or stroke, the overall benefit in primary prevention is largely neutralized by its side effects. A genetic variant in GUCY1A3 has been linked to coronary risk and impaired inhibition of platelet aggregation. In post hoc analyses of subsets from two randomized, placebo-controlled, trials of aspirin in primary prevention of cardiovascular disease, the Women’s Genome Health Study and the Physician’s Health Study, we found that homozygous carriers of the GUCY1A3 coronary artery disease risk-allele benefited from randomized aspirin treatment in primary prevention. Individuals of the other genotypes did not benefit or even experience harm.

Clinical Implications (MUST be limited to 40 words and accessible to a lay audience) - please describe the clinical implications of your research.*

Knowledge of GUCY1A3 genotype might be used to inform decision-making for aspirin prescription in primary prevention in low- and intermediate-risk patients.

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First Name*: Florencia

Last Name*: Halperin

Academic Degrees*: MD

BWH Department*: Medicine

BWH Division (if applicable)*: Endocrinology, Diabetes & Hypertension

BWH ID Number: 

Email Address*: fhalperin@bwh.harvard.edu

BWH Title or HMS Rank (if relevant)*: Co-Director, Center for Weight Management and Metabolic Surgery, Brigham and Women’s Hospital; Instructor in Medicine, Harvard Medical School

Twitter Handle (if applicable): 

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If you selected 'other' please specify your research area:

Title*: Cardiometabolic and Patient-Reported Outcomes in Obese T2D Patients 3 Years after Randomization to Laparoscopic Adjustable Gastric Band (LAGB) vs. Intensive Diabetes and Medical Weight Management (IMWM)
Abstract Body (MUST be limited to 200 words, anything beyond 200 words will be truncated for print)*

Few randomized trials have compared bariatric surgery to intensive medical diabetes and weight management. We randomized 40 subjects (22M/18F; BMI 36.5±3.7 kg/m2; age 51±10 yrs; HbA1c 8.2±1.2 %) to either LAGB (n = 18) or a 12-week IMWM program (n = 22) with 3 yrs follow-up. Weight loss after LAGB was greater at 1 yr (-13.5±1.3 vs. -8.4±1.2 kg, p < 0.01), and 3 yrs (-12.0±2.0 vs. -4.8±2.0 kg, p<0.01). HbA1c reduction was similar at 1 yr (-1.2±0.3 vs. -1.0±0.3 % at 1 yr.), but sustained after LAGB at 3 yrs (-0.8±0.4 %, p<0.05 vs. baseline) (IMWM +0.2±0.4 %, p=NS). HDL increased more (all times) after LAGB (+10.0±1.7 vs. +2.6±2.7 mg/dl at 3 yrs, p<0.01). Changes in TG, LDL and BP did not differ. Self-reported health status (SF-36 physical, mental, total scores) changed minimally and comparably from baseline. Impact of Weight on Quality of Life (IWQOL) and Problem Areas in Diabetes (PAID) improved significantly and similarly after both interventions (p<0.01). In sum LAGB leads to 1) greater sustained weight loss, 2) improved HbA1c, and 3) higher HDL.

Lay Summary (MUST be limited to 200 words, anything beyond 200 words will be truncated for print). Please keep in mind - Discover Brigham is open to the public, this lay summary needs to be appropriate for lay audiences with NO scientific background. *

While previous studies have demonstrated that bariatric surgery is effective in treating obesity, and leads to improved blood sugar control or remission of type 2 diabetes (T2D), few prospective randomized trials have directly compared the long-term efficacy and durability of specific bariatric procedures to an intensive medical and lifestyle intervention program. The goal of our study was to compare clinical, cardiometabolic, and patient-reported outcomes in obese patients with T2D three years after randomization to laparoscopic adjustable gastric banding (LAGB) or an intensive multi-disciplinary diabetes and medical weight management program (IMWM). We showed that after 3 years, LAGB leads to 1) greater sustained weight loss, 2) improved blood sugar control as measured by Hemoglobin A1c, and 3) higher HDL ("good") cholesterol. Changes in triglycerides, LDL ("bad") cholesterol, and blood pressure, as well as self-reported health measures, were similar in both groups. These findings may help guide patients with obesity and T2D when exploring options for diabetes and weight management.

Clinical Implications (MUST be limited to 40 words and accessible to a lay audience) - please describe the clinical implications of your research.*

Compared to IMWM, at 3 years LAGB leads to greater weight loss, reduction in antidiabetic medications, and increase in HDL in T2D and obesity. Our findings may help guide patients and physicians choosing treatments for weight and glycemic control.

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- Lung Research
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- Regenerative Medicine
- Women's Health & Gender Biology

If you selected 'other' please specify your research area:

Title*
Sleeve Gastrectomy restores mucosal CD8+ T-cell immunity.

Authors*
David A Harris MD, Renuka Subramaniam PhD, Keyvan Heshmati MD, Ali Tavakkoli MD, Eric Sheu MD PhD

PI*
Eric Sheu MD PhD

Abstract Body (MUST be limited to 200 words, anything beyond 200 words will be truncated for print)*
Background: Gut milieu changes underlie the benefits of sleeve gastrectomy (SG), which are possibly realized through the mucosal immune system. Thus, we hypothesized that jejunal lymphocyte populations contribute to diabetes resolution and weight loss following SG. Methods: C57Bl/6J mice were placed into four groups – normal chow diet (lean; n=6); high fat diet (Obese; n=6); Obese Sham (n=7); Obese SG (n=6). Glucose and insulin tolerance were assessed. Jejunums were harvested for time of flight mass cytometry (CyTOF) and visualization of stochastic neighbor embedding (ViSNE) was used for unbiased population identification. Results: Compared to Lean mice, Obese mice have perturbation in multiple jejunal lymphocyte populations including a reduction (85±7 vs 37±10%; p=0.003) in jejunal CD8+CD103+ tissue resident memory T-cells (TRM). TRM are responsible for rapid pathogen defense at mucosal surfaces. Of the 40 distinct lymphocyte populations assessed, ViSNE revealed that only changes in jejunal TRM correlated with improved weight and insulin sensitivity following SG. SG repairs this obesity-induced mucosal immune defect by restoring jejunal TRM to Lean levels (66±14%). Conclusions: Obesity disrupts intestinal immunity leading to insulin resistance. SG reverses the deficit in jejunal TRM seen in obesity and thereby restores protective intestinal immune function, which may contribute to its metabolic benefits.

Lay Summary (MUST be limited to 200 words, anything beyond 200 words will be truncated for print). Please keep in mind - Discover Brigham is open to the public, this lay summary needs to be appropriate for lay audiences with NO scientific background. *

Obesity is a major threat to human life and is marked by chronic inflammation leading to diseases such as Type 2 Diabetes. Bariatric surgery is the most effective therapy for patients suffering with obesity. Sleeve Gastrectomy has become the most performed bariatric surgery owing to its effectiveness and safety. This procedure entails removal of a portion of the stomach so that the remaining stomach resembles a tube. The reasons why this surgery is successful remain unknown but our lab believes that the immune system may play a substantial role in the realization of these improvements. In this study, we found that obesity is associated with multiple changes in the gut immune system. This includes specific changes in small bowel memory t cells, which are normally responsible for rapid destruction of invading bacteria and viruses. Interestingly, we show that there is a normalization of this small bowel memory t cell population following sleeve gastrectomy and further, that these changes were the only changes that paralleled the improvements in obesity and diabetes. Thus, understanding the function of these memory cells following surgery may hold the key to developing novel therapies for obesity and related diseases.

Clinical Implications (MUST be limited to 40 words and accessible to a lay audience) - please describe the clinical implications of your research. *

Bariatric surgery reverses impairments in small bowel memory t cells, which is associated with weight loss and improvements in diabetes. A better understanding the role of these cells following surgery may lead to novel therapies for obesity and related diseases.

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Examining Genetic and Hormonal Environment Differences to Establish a Model of Sex Differences in the Brain Using Human iPSC Technology

Many neurological diseases show preferential risk development in males and females, with males having a higher incidence of ADHD, Parkinson's disease, schizophrenia and autism while females have higher risk of major depressive disorder, anxiety disorders, multiple sclerosis and Alzheimer’s disease. There has been clear evidence of sexually dimorphic molecular and morphological phenotypes in adult brains that are a result of intrinsic genetic differences caused by female (XX) or male (XY) chromosomes as well as the production of exogenous steroid hormones. Here, we are studying these sex differences using human iPSC-derived neurons as a model to analyze gene expression profiles and morphological changes during neuronal development. To study intrinsic genetic differences induced by sex chromosomes, we have analyzed neurons derived from multiple male and female donors. Additionally, we are using iPSC-differentiated neurons to examine the responsiveness of neurons to exogenous androgen and estrogen at multiple stages of development, while also analyzing the levels of endogenous steroid hormones produced by the cells. Finally, gene expression profiles post-hormone exposure have been obtained. RNA sequencing has revealed several genes that are differentially expressed in males versus females, as well as genes induced by induction of estradiol and/or testosterone.
Sex differences in the brain play a crucial role in the prevalence and development of many neurological diseases. Males experience a higher risk of ADHD, Parkinson's disease, schizophrenia, and autism, while females have a higher risk of major depressive disorder, anxiety disorders, multiple sclerosis, and Alzheimer's disease, to name a few. Biological factors contribute to this sex bias in risk due to the presence of two X chromosomes in females and one X and one Y chromosome in males. Variations in these genetic backgrounds lead to the involvement of different sex-related genes and hormones, which contribute to unique sex-based neurological characteristics. Our lab employs human stem cell technology to create a controlled system for defining and characterizing sex differences in the brain at the cellular level, by examining the effects of these genes and hormones on human neuronal development. We are currently generating genetically identical male and female cells to isolate and analyze the chromosomes responsible for sex determination. We have also produced neurons from human stem cells to study responses to sex steroid hormones in brain development. Our preliminary results show that we can model differences in gene and hormonal effects associated with sex in our stem-cell-generated neurons.

Clinical Implications (MUST be limited to 40 words and accessible to a lay audience) - please describe the clinical implications of your research.*

Sex differences contribute to risk variance in males and females for many neurological diseases and may also result in response differences to therapeutic interventions. Understanding these differences could help develop sex-specific medicine, that includes personalized medicine for males and females.
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<td>Research fellow/Trainee</td>
<td>@juanph19</td>
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**If you selected 'other' please specify your research area:**

**Title***
Beyond Mortality: Routine Inclusion of Long-term Functional and Patient Reported Outcomes (PROs) into Trauma Registries

**Authors***

**PI***
Adil H Haider
Objective: The National Academies of Science, Engineering, and Medicine recently recommended inclusion of post-discharge Patient-Reported Outcomes (PROs) as metrics to benchmark the quality of trauma care. Currently, these measures are not routinely collected at most trauma centers. We sought to determine the feasibility and value of adding long-term PROs measures to trauma registries.

Methods: Trauma patients with moderate or severe injuries (Injury Severity Score ≥9), admitted to three Level-I trauma centers in Boston were identified and contacted 6 or 12-months post-injury to participate in a telephone interview evaluating: Quality-of-Life, Post-Traumatic Stress Disorder (PTSD), and return to work. Results: Data were collected for 844 (41%) of 2,041 eligible patients. Among participants, half reported to have pain daily, 42% had not yet returned to work, 37% have functional limitation for at least one activity of daily living, and 23% screened positive for PTSD. There were significant reductions (p<0.001) in SF-12 physical composite score [mean (SD): 42(11.4)] relative to population norms [mean (SD): 50(10)]. Conclusions: Measuring long-term PROs after traumatic injuries is feasible and uncovered a significant level of impairment. Routine collection of such data characterizes trauma outcomes beyond mortality and will enable the development of quality improvement metrics that better reflect patients’ post-injury experience.

Lay Summary (MUST be limited to 200 words, anything beyond 200 words will be truncated for print). Please keep in mind - Discover Brigham is open to the public, this lay summary needs to be appropriate for lay audiences with NO scientific background. *

Objective: Patient-reported measures of long-term outcomes (PROs) are necessary to help patients, family members and providers make health decisions that are informed by patients’ individual preferences, goals and expectations. Currently, these measures are not routinely collected at most trauma centers. We sought to determine the feasibility and value of adding long-term PROs measures to trauma registries. Methods: Trauma patients with moderate or severe injuries admitted to three trauma centers in Boston were identified and contacted 6 or 12-months post-injury to participate in a telephone interview evaluating: Quality-of-Life, Post-Traumatic Stress Disorder (PTSD), and return to work. Results: Data were collected for 844 (41%) of 2,041 eligible patients. Among participants, half reported to have pain daily, 42% had not yet returned to work, 37% have functional limitation for at least one activity of daily living, and 23% screened positive for PTSD. There was significant reduction in overall physical health relative to population norms. Conclusions: Measuring long-term PROs after traumatic injuries is feasible and uncovered a significant level of impairment. Routine collection of such data characterizes trauma outcomes beyond mortality and will enable the development of quality improvement metrics that better reflect patients’ post-injury experience.

Clinical Implications (MUST be limited to 40 words and accessible to a lay audience) - please describe the clinical implications of your research.*

Understanding long-term Patient-Reported Outcomes (PROs) is important for identifying patients at risk for poor long-term outcomes that are meaningful for patients. Long-term PROs will improve care quality and value.

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SliceTracker: An open source 3D Slicer extension for supporting transperineal in-bore MRI-guided targeted prostate biopsy

Prostate Cancer (PCa) is one of the most common causes of cancer deaths in the USA. Transperineal MRI-guided targeted prostate biopsy (tpMRgBx) has a low risk of infection, high rate of detecting significant PCAs, and is well tolerated by patients. tpMRgBx involves biopsy planning, correlation with the patient’s coordinate system, targeting, segmentation, deformable registration and evaluation. Until recently, tpMRgBx procedure, as implemented at the BWH, relied on custom, closed source software tools developed over a decade ago. Our goal was to develop a free open source 3D Slicer extension to support tpMRgBx continuing earlier work, and perform its comparison with the previously used approach by analyzing timestamps of collected data during past procedures (n=20 for each approach), and measuring the time from receiving the initial intra-procedural image to the time when re-identified targets become available to the operator. SliceTracker combines all tpMRgBx steps into one single workflow aiming for improved usability. The time to provide target locations to the operator was significantly lower for SliceTracker (p<0.01) as compared to the previous implementation: median time was reduced from 6.6 min (range 4.6-32.7 min) to 3.6 min (range 1.4-17.7 min).

Lay Summary (MUST be limited to 200 words, anything beyond 200 words will be truncated for print). Please keep in mind - Discover Brigham is open to the public, this lay summary needs to be appropriate for lay audiences with NO scientific background. 

Prostate Cancer (PCa) is one of the most common cancers in the USA. Histological analysis of a tissue sample obtained with a biopsy needle is required for diagnosing PCa. Targeted biopsy is a technique that aims to collect tissue sample(s) from the area of the prostate that is appearing suspicious in Magnetic Resonance Imaging
MRI. We develop research software that can assist the clinician in performing transperineal (needle incisions are made through the perineum instead of the rectum) targeted biopsy inside the MRI scanner bore. Transperineal approach has lower rate of infection compared with the transrectal biopsy. Performing the needle insertion inside the scanner bore potentially leads to improved accuracy. Our software approach is implemented within the open source 3D Slicer (http://slicer.org) platform. It includes functionality that supports image visualization, needle guidance, and re-identification of the suspected cancer locations in the intra-procedural images based on the diagnostic MRI performed in advance of the procedure. The software has been used to support clinical research in over 100 targeted prostate biopsy cases, and demonstrated significant improvement over an earlier version in terms of the time needed to provide the interventionalist with the target locations.

Clinical Implications (MUST be limited to 40 words and accessible to a lay audience) - please describe the clinical implications of your research.*

The results show about 50% reduction in time needed for re-identification of PCa target(s) as compared to the original implementation. SliceTracker successfully replaced the old approach and has been used in over 100 prostate biopsies.

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If you selected 'other' please specify your research area:

Title*
Weight-loss independent Type 2 Diabetes Resolution Following Sleeve Gastrectomy

Authors*
Keyvan Heshmati MD, David Harris MD, Ashley Vernon MD, Malcolm Robinson MD, Scott Shikora MD, Ali Tavakkoli MD, Eric Sheu MD, PhD

PI*
Eric Sheu MD, PhD

Abstract Body (MUST be limited to 200 words, anything beyond 200 words will be truncated for print)*
Background Weight-loss independent type 2 Diabetes (T2D) resolution following Roux-en-Y gastric bypass (RYGB) is well-established. However, whether sleeve gastrectomy (SG) has a weight-loss independent impact on T2D is controversial. Methods A prospectively maintained, single institution database was used to collect demographic, clinical, and T2D medication data on patients before and after SG and RYGB between 2010-2015 (n=182 per group). Chi² or two-tailed Student’s t-tests were used were appropriate. Results No significant differences were found in baseline characteristics and T2D medication requirements. HbA1c was lower pre-SG (7.20±1.29) compared to RYGB (7.52±1.33, p = 0.02). At discharge, more patients who underwent SG (38%) were off all T2D medications compared to RYGB (24%, p=0.003). At 2 weeks, a comparable proportion of SG and RYGB patients no longer required T2D medications (37% vs 48%, p=0.18). At 3 months, SG patients experienced only mild additional T2D improvement despite continued weight loss; whereas, RYGB patients continued to show improvement (SG: 45%, RYGB: 62%, p=0.002). Conclusion SG leads to improvements in T2D within days of surgery, which is comparable in magnitude to RYGB. This data suggests that both SG and RYGB activate weight-loss independent mechanisms of T2D resolution.

Lay Summary (MUST be limited to 200 words, anything beyond 200 words will be truncated for print). Please keep in mind - Discover Brigham is open to the public, this lay summary needs to be appropriate for lay audiences with NO scientific background.

Background Weight-loss independent type 2 Diabetes (T2D) resolution following Roux-en-Y gastric bypass (RYGB) is well-established. However, whether sleeve gastrectomy (SG) has a weight-loss independent impact on T2D is controversial. Methods Demographic, clinical, and T2D medication data on patients before and after SG and RYGB between 2010-2015 was collected (n=182 per group). Results No significant differences were found in baseline characteristics and T2D medication requirements. HbA1c which is an indicator for blood sugar control in the past 3 months, was lower pre-SG (7.20±1.29) compared to RYGB (7.52±1.33, p = 0.02). At discharge, more patients who underwent SG (38%) were off all T2D medications compared to RYGB (24%, p=0.003). At 2 weeks, a comparable proportion of SG and RYGB patients no longer required T2D medications (37% vs 48%, p=0.18). At 3 months, SG patients experienced only mild additional T2D improvement despite continued weight loss; whereas, RYGB patients continued to show improvement (SG: 45%, RYGB: 62%, p=0.002). Conclusion SG leads to improvements in T2D within days of surgery, which is comparable in magnitude to RYGB. This data suggests that both SG and RYGB activate weight-loss independent mechanisms of T2D resolution.

Clinical Implications (MUST be limited to 40 words and accessible to a lay audience) - please describe the clinical implications of your research.

This study was designed to understand the physiology of the weight-loss independent diabetes resolution after Sleeve Gastrectomy.

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- Pregnancy & Fertility
- Women's Health & Gender Biology
- Trauma
- Other

If you selected 'other' please specify your research area:

Title*
Improvements to a hit compound that increases SMN2 expression for SMA

Authors*
Dawid K. Fiejtek

PI*
Kevin J. Hodgetts

Abstract Body (MUST be limited to 200 words, anything beyond 200 words will be truncated for print)*
Spinal Muscular Atrophy (SMA) is a neurogenerative disease that is caused by low levels of survival motor neuron (SMN) protein due to a mutation in the SMN1 gene. An SMN2-luciferase reporter assay was developed to identify compounds
that stabilize the SMN protein or act during transcription of the SMN2 gene. One hit compound, a 3,4-dihydro-4-phenyl-2(1H)-quinolinone derivative, had an EC50 of 8.3 μM (186%) and increased the activity of the assay by 2.8-fold. Different analogs were synthesized to study the structure-activity relationship (SAR) of the hit compound to increase the activity. There has been success in the SAR study with the most active analog having an EC50 of 4.1 μM (263%). The most active analog is racemic and it was separated by chiral chromatography into its two enantiomers. The two enantiomers were studied in an SMN2 reporter assay, it was discovered that one enantiomer was active and the other was inactive. Currently, the stereochemistry of the active enantiomer is unknown. The synthesis of new analogs to improve both activity and to elucidate the stereochemistry of the active enantiomer is in progress.

**Lay Summary (MUST be limited to 200 words, anything beyond 200 words will be truncated for print). Please keep in mind - Discover Brigham is open to the public, this lay summary needs to be appropriate for lay audiences with NO scientific background.**

Spinal Muscular Atrophy (SMA) is a heritable disease that is one of the leading genetic causes of infant death worldwide. This neurodegenerative disease is caused by low levels of a protein called survival motor neuron (SMN), which is caused by a mutation in a gene called SMN1. The low level of SMN protein is characterized by loss of muscle function and death. There are four types of SMA. Type I is the most severe due to infants not being able to sit unsupported and death occurs within two years of life. Infants with type II can sit unsupported but never gain the ability to walk independently. Type III and IV are milder forms of the disease with patients living regular lifespans but with various disabilities and loss of motor function over time. There are currently no affordable treatments or cures for SMA, and this research is trying to find new treatments for SMA.

**Clinical Implications (MUST be limited to 40 words and accessible to a lay audience) - please describe the clinical implications of your research.**

The hit is the starting point to new treatments for SMA. We are using medicinal chemistry to improve the efficacy of new analogs and identify compounds suitable for studies in mouse models of SMA and ultimately advance into clinical trials.

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- Trauma
- Women's Health & Gender Biology
- Other

If you selected 'other' please specify your research area:
Medical education,
Ophthalmology

Title*
Outcomes of Funded Ophthalmological Research Opportunities for Medical Students

Authors*
Joy Jin*, Nico Kahl*, Grace Young, Achyut Patil, Bryan Iorgulescu M.D. *denotes co-first authors

PI*
J. Bryan Iorgulescu, M.D.

Abstract Body (MUST be limited to 200 words, anything beyond 200 words will be truncated for print)*

Background: Dwindling research funding and increased clinical pressures are a challenge to fostering physician-scientists in ophthalmology. Several medical student ophthalmology research fellowships are available, but their impact on career trajectories remains unknown. Methods: Programs were systematically queried to identify funded summer research opportunities for medical students. Outcomes were ascertained from NIH reporter, NPIs, LinkedIn, Doximity,
Comparisons of proportions were assessed by Fisher’s exact and Chi2 tests, as appropriate. Results: 4 ophthalmology-specific medical student fellowship programs were identified with 141 awardees since 1993. 2 were 12-week-long programs, with 28 awardees since 2011, 52% (12/23) have entered the match, 25% (3/12) of whom matched into ophthalmology. None of the currently practicing awardees from 12-week programs have NIH funding. 2 were 52-week-long programs, with 114 awardees since 1993, ~79% (84/106) of whom matched into ophthalmology. 6 of the currently practicing awardees have NIH funding, with a median award of $317,398, and 51% (40/78) are in private practice. The overall SFmatch ophthalmology match rate for 2016 was 1.6%. Conclusions: Medical students may pursuing year-long ophthalmology research fellowships to increase their competitiveness for matching. Long-term mentored funded research in ophthalmology is significantly associated with students entering ophthalmology and academic practice.

**Lay Summary (MUST be limited to 200 words, anything beyond 200 words will be truncated for print). Please keep in mind - Discover Brigham is open to the public, this lay summary needs to be appropriate for lay audiences with NO scientific background.**

Dwindling research funding and increased clinical pressures are a challenge to increasing the numbers of physician-scientists in medicine. Several medical student ophthalmology research fellowships are available, but their impact on career trajectories remains unknown. Our study investigates the roles that these early, funded and, mentored research opportunities have in medical student’s career choices and opportunities. We found that medical students who engaged in year-long ophthalmology research fellowships later in their medical schooling overwhelmingly continued to enter the field of ophthalmology, and significantly so when compared to medical students who only engaged in summer-long ophthalmology research fellowships earlier in their medical schooling. Our findings suggest that medical students be may pursuing year-long ophthalmology research fellowships to increase their competitiveness for matching into ophthalmology but were also associated with a higher rate of academic practice.

**Clinical Implications (MUST be limited to 40 words and accessible to a lay audience) - please describe the clinical implications of your research.**

Our findings help identify cost-effective early interventions for encouraging medical students to pursue academic and physician-scientist careers, particularly given the many contemporary challenges facing physician-scientists and the specialty of ophthalmology.

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Sunil  Kapur  MD

BWH Department*  BWH Division (if applicable)  BWH ID Number
Medicine  Cardiology  100295430

Email Address*  BWH Title or HMS Rank (if relevant)*
skapur@bwh.harvard.edu  Instructor

Twitter Handle (if applicable)

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Title*
Novel Phenotyping of Heart Failure with Perserved Ejection Fraction

Authors*  PI*
Sunil Kapur, Calum Macrae  Calum Macrae

Abstract Body (MUST be limited to 200 words, anything beyond 200 words will be truncated for print)*
We prospectively studied 159 patients with left ventricular hypertrophy (LVH) and heart failure with preserved ejection fraction (HFpEF) who presented to a tertiary care cardiovascular clinic and performed detailed clinical, laboratory, ECG, and echocardiographic phenotyping of the study participants. After informed consent, we systematically evaluated these patients with a predefined series of rapid, non-invasive bedside physiologic measurement tools. We evaluated the role of these unrelated, novel non-cardiovascular physiologic measures and their ability to stratify LVH/HFpEF with regards to etiology as well as prognosis. Our analyses demonstrated that non-invasive peripheral nerve autonomic function discriminated AL cardiac amyloid as the etiology of HFpEF when compared to patient populations with hypertrophic cardiomyopathy, benign left ventricular hypertrophy and transthyretin (TTR) amyloid. Furthermore, evaluation with auditory brainstem response appeared to provide a bedside discrimination between TTR amyloid from other etiologies of LVH. Balance assessment differences between eyes open and closed identified patients with hypertrophic cardiomyopathy had a unique pattern when compared to other etiologies of LVH. Furthermore, among patients with benign LVH, impaired peripheral nerve function and impaired balance measures were correlated with symptoms of heart failure as measured by New York Heart Association classification.

Lay Summary (MUST be limited to 200 words, anything beyond 200 words will be truncated for print). Please keep in mind - Discover Brigham is open to the public, this lay summary needs to be appropriate for lay audiences with NO scientific background.*

Left ventricular hypertrophy (LVH) is a term for an enlarged heart muscle, and is a common diagnosis in patients with heart disease. When the enlarged muscle fails to adequately pump blood, heart failure with preserved ejection fraction (HFpEF) can develop, which results in significant symptoms for the patient. These diseases can develop for a number of different reasons, and the cause of the problem indicates the best course of treatment and expected prognosis. With traditional cardiovascular risk factors and imaging, to date, there is no clinical risk stratification scheme that efficiently stratifies causes of LVH/HFpEF. We sought to systematically evaluate the role of novel digital markers in the diagnosis and management of HFpEF in consecutive patients presenting to an outpatient cardiology clinic. We identified that measures of other organ systems could in fact inform cardiovascular disease. Surprisingly, measures of hearing, skin nerves and lower body balance could stratify patients with LVH/HFpEF by their distinct cause. Importantly, these rapid, non-invasive tests may potentially allow for immediate bedside diagnosis of conditions that were previously difficult to understand.

Clinical Implications (MUST be limited to 40 words and accessible to a lay audience) - please describe the clinical implications of your research.*

This study identifies methods to discriminate etiologies of heart failure with rapid bedside testing. Peripheral nerve function, acoustic evoked potentials and balance assessment may be helpful in stratifying the cause and prognosis of this patient population.

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First Name* 
Srijesa

Last Name* 
Khasnabish

Academic Degrees* 
BA

BWH Department* 
General Medicine

BWH Division (if applicable) 
General Internal Medicine

BWH ID Number 
100480389

Email Address* 
skhasnabish@bwh.harvard.edu

BWH Title or HMS Rank (if relevant)* 
Research Assistant

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- Women's Health & Gender Biology

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Title*
Modifying Fall TIPS Fall Prevention Toolkit for Psychiatric Inpatient Settings

Authors*
Khasnabish, S

PI*
Dykes, PC

Abstract Body (MUST be limited to 200 words, anything beyond 200 words will be truncated for print)*
Motivation: The consequences of inpatient falls can range from delayed course of treatment to serious injury. Studies have shown that fall-related injury rates in psychiatric/geropsychiatric units are higher than others. Our team developed and tested the Fall TIPS (Tailoring Interventions for Patient Safety) Toolkit (FTTK) at Brigham and Women's Hospital. We found that the FTTK supports the 3-step fall prevention process: 1) Risk assessment, 2) tailored care planning, and 3) consistent implementation of the fall prevention plan. While FTTK effectively prevents falls on medical/surgical units, no such tool exists for psychiatric inpatients. The purpose of this literature review is to inform refinement of the FTTK for use with psychiatric inpatients.

Methods: We conducted a systematic literature review in PubMed and CINAHL using MeSH terms. We reviewed 379 article abstracts to identify fall prevention evidence specific to psychiatric settings. Results: Limited evidence related to the 3-step fall prevention process was found. Three fall risk assessments were identified, all with flaws in validation process. No evidence-based interventions were identified. Conclusions/Implications: Based on our literature review, there is a gap in fall prevention evidence specific to psychiatric inpatients. Next steps include working with stakeholders to identify requirements for modifying the FTTK for use in psychiatric settings.

Lay Summary (MUST be limited to 200 words, anything beyond 200 words will be truncated for print). Please keep in mind - Discover Brigham is open to the public, this lay summary needs to be appropriate for lay audiences with NO scientific background. *

Patient falls in the hospital are a common cause of harm. Our research developed the Fall TIPS Toolkit (FTTK). We found that the FTTK prevented falls using a 3-step process. 1) talking to the patient about their risks for falling. 2) Creating a personalized fall prevention plan with the patient. 3) Making sure the plan is followed consistently. This 3-step process works well for patients on medical and surgical units. It has not been used to prevent falls in patients with mental health problems. We are working on improving the FTTK to meet the needs of these patients. There is very limited research done in the area. We plan to work with mental health patients, family, and care providers to learn what works best to help this patient population.

Clinical Implications (MUST be limited to 40 words and accessible to a lay audience) - please describe the clinical implications of your research.*

A refined version of Fall TIPS can then be tested in psychiatric settings to establish an evidence base for reducing fall rates in this patient population.

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**Title**

Cytomegalovirus infection stimulates tumor cell–pericyte crosstalk to facilitate angiogenesis and tumor growth in glioblastoma

**Authors**

Harald Krenzlin, Korneel Grauwet, Hong Zhang, Prajna Behera, Marion B Griessl, Michael Gutknecht, Lai Ding, Charles H Cook, E Antonio Chiocca, Sean Lawler

**PI**

Sean Lawler

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**Abstract Body (MUST be limited to 200 words, anything beyond 200 words will be truncated for print)**
Introduction: Cytomegalovirus (CMV) has been linked to glioblastoma for over a decade, but is still lacking a definite underlying pathogenic mechanism. Methods: This study investigates CMV expression in human glioblastoma samples and characterizes a new CMV latent, orthotopic glioblastoma mouse model. RNAseq, and in vitro functional assays were used to investigate mechanisms. Results: Immunostaining of patient samples identified viral antigens expressed in multiple cellular compartments including the novel observation of co-localization with pericytes. RNAseq of human brain vascular pericytes (HBVPs) and glioblastoma stem-like cells (GSCs) revealed upregulation of proangiogenic cytokines after CMV infection. Medium from infected GSCs/HBVPs led to tube formation on Matrigel and aortic ring assays in vitro. PDGF-DD, upregulated by CMV, was identified as a driver of angiogenesis and HBVP migration. Orthotopic injection of GI261fluc murine glioblastoma cells in CMV latent mice, caused intratumoral virus reactivation and shortened survival rates (p=0.0004). Infected tumours showed significantly higher numbers of infiltrating- and blood vessel-associated pericytes. CMV treatment with antiviral drug Cidofovir can reduce vascularization and extend the overall survival. Conclusion: In patient-derived tumor samples CMV partially co-localizes with perivascular pericytes. Tumor growth and vascularization is increased in murine glioblastoma models in the context of latent CMV infection, driven by PDGF-DD.

Lay Summary (MUST be limited to 200 words, anything beyond 200 words will be truncated for print). Please keep in mind - Discover Brigham is open to the public, this lay summary needs to be appropriate for lay audiences with NO scientific background. *

Progress in the treatment of glioblastoma (GBM) over the last few decades has remained marginal and GBM is still universally fatal with short survival times after initial diagnosis. Identification of targets is crucial for the development of new therapeutic strategies. CMV is one of the most common herpes viruses with more than 60% of the population being infected and has been associated with GBMs for over a decade. In this study, CMV is detected in patient derived tumor samples, predominantly associated to the space around tumor vessels. Knowledge from this analysis is used to create a mouse model to understand disease mechanisms and test new treatment methods. We discovered that CMV infection leads to more rapid and increased vascularization in GBMs, thus shortening the animal survival. Platelet derived growth factor delta is upregulated by CMV infection and has been identified as driver to ensure tumor blood supply. Treating CMV infection in mice reduces tumor blood supply and increases the overall survival time. In summary, here we present new insight into the interrelation of GBMs with the herpes virus CMV and how it might influence tumor growth and development. Furthermore, we establish CMV as promising new drug target in GBM therapy.

Clinical Implications (MUST be limited to 40 words and accessible to a lay audience) - please describe the clinical implications of your research.*

Despite high therapeutic cost and efforts, GBM is still universally fatal with short survival times after initial diagnosis. We identified CMV as potential drug target for supportive antiviral therapy to increase survival times in GBM.

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First Name*  Valentina

Last Name*  Lagomarsino

Academic Degrees*  BA

BWH Department*  Neurology

BWH Division (if applicable)  BTM 10012

BWH ID Number  100435439

Email Address*  vlagomarsino@bwh.harvard.edu

BWH Title or HMS Rank (if relevant)*  Research Assistant

Twitter Handle (if applicable)

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Stem Cells

Title*
Using Human Derived Neural Cells to Predict Alzheimer’s disease

Authors*
Valentina Lagomarsino, Priya Srikanth, Christina R. Muratore, Steven Ryu, Amy He, Constance Zhou, Walter Taylor

PI*
Tracy Young Pearse

Abstract Body (MUST be limited to 200 words, anything beyond 200 words will be truncated for print)*
More than 5 million Americans are currently living with Alzheimer’s disease. Because of the overwhelming evidence suggesting the importance of Aβ to the disease state, billions of dollars have been spent to develop and test therapeutics that target Aβ, and while most of them did modestly slow cognitive decline, many of these drugs failed during clinical trials. We have generated a resource to probe the heterogeneity of late onset Alzheimer’s disease using human pluripotent stem cells.
New stem cell technology has allowed for the opportunity to study neurodevelopmental diseases by generating 3D structures, cerebral organoids, that resemble human brains. Here, we have used this approach to study the gene, DISC1, which has been associated with psychiatric disorders based on genetic studies. Our DISC1 mutated 'tiny brains' display disorganized structural morphology and altered gene expression. This phenotype can be induced in our wild-type organoids by WNT agonism, which is involved in neuronal migration. This study is one of the first to use this technology to model a psychiatric disorder and gene expression changed have opened up new avenues for future studies.

Clinical Implications (MUST be limited to 40 words and accessible to a lay audience) - please describe the clinical implications of your research.

Shared gene expression changes, with DISC1 and WNT agonism, suggest mechanisms for the observed morphologic dysregulation and open up new avenues for future studies which could eventually lead us to pinpoint early changes in brain development in patients with psychiatric-disorders.
First Name*  
Véronique

Last Name*  
Latreille

Academic Degrees*  
PhD

BWH Department*  
Neurology

BWH Division (if applicable)  

BWH ID Number  

Email Address*  
vlatreille@bwh.harvard.edu

BWH Title or HMS Rank (if relevant)*  
Postdoctoral research fellow

Twitter Handle (if applicable)

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- Genomics
- Immunology/Rheumatology
- Lung Research
- Neurosciences
- Patient-Centered Outcomes/Comparative Effectiveness
- Regenerative Medicine
- Women's Health & Gender Biology

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Title*  
Seizures from sleep are associated with more severe hypoxemia and increased risk of postictal generalized EEG suppression

Authors*  
Véronique Latreille, Myriam Abdennadher, Barbara Dworetzky, Judith Ramel, David White, Eliot Katz, Marcin Zarowski, Sanjeev Kothare, and Milena Pavlova

PI*  
Milena Pavlova

Abstract Body (MUST be limited to 200 words, anything beyond 200 words will be truncated for print)*
Epilepsy patients have a more than 20-fold greater risk of death (sudden unexpected death in epilepsy, SUDEP) when compared to the general population. SUDEP often occurs at night or in relation to sleep. In this study, we examined oxygen saturation before, during, and after seizures occurring either during sleep or wakefulness in adult epilepsy patients. Respiratory measures were examined in 48 recorded seizures (sleep, n = 23 and wake, n = 25) from 20 epilepsy patients. Results show that seizures from sleep were associated with lower saturation, as compared to seizures from wakefulness, both during ictal (sleep median = 90.8; wake median = 95.5, p < 0.01) and postictal periods (sleep median = 94.3; wake median = 96.9, p = 0.05). Seizures from sleep were also associated with a larger desaturation drop (sleep median = -4.2; wake median = -1.2, p = 0.01). Postictal generalized electroencephalographic suppression (PGES) occurred more frequently after seizures from sleep (39%) relative to wake-related seizures (8%, p = 0.01). Our findings suggest that nocturnal seizures may entail a higher SUDEP severity burden, as they are associated with more severe and longer hypoxemia events, and more frequently followed by PGES, both factors implicated in sudden death.

**Lay Summary (MUST be limited to 200 words, anything beyond 200 words will be truncated for print). Please keep in mind - Discover Brigham is open to the public, this lay summary needs to be appropriate for lay audiences with NO scientific background.**

Sudden unexpected death in epilepsy (SUDEP) is one of the leading causes of death in adult individuals with epilepsy. These persons have a more than 20-fold greater risk of death when compared to the general population. SUDEP most often occurs at night or in relation to sleep. The current study aimed to investigate whether nocturnal seizures are more likely to be associated with respiratory compromise, such as more severe oxygen desaturation as compared to seizures from wakefulness. We examined oxygen saturation before, during, and after seizures occurring either during sleep or wakefulness in adult epilepsy patients undergoing long term video-EEG monitoring at Brigham and Women’s Hospital. Respiratory measures were examined in 48 recorded seizures (sleep, n = 23 and wake, n = 25) from 20 adult epilepsy patients. Results showed that seizures from sleep were associated with a lower oxygen saturation and larger desaturation drop (from baseline), as compared to seizures from wakefulness, both during ictal and postictal periods. Postictal generalized electroencephalographic suppression (PGES) occurred more frequently following seizures from sleep than wakefulness. Our findings suggest that nocturnal seizures are associated with more severe and longer hypoxemia events, and more frequently followed by PGES, both factors implicated in sudden death.

**Clinical Implications (MUST be limited to 40 words and accessible to a lay audience) - please describe the clinical implications of your research.**

Our findings highlight the importance of nocturnal monitoring of epilepsy patients, as well as of simultaneous recording of respiratory functions (including oxygen saturation) with electroencephalography (EEG) during epilepsy workup, to identify patients at risk of sudden death.

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<tr>
<td>Annie</td>
<td>Lewis-O’Connor</td>
<td>PhD, NP, MPH</td>
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<tbody>
<tr>
<td><a href="mailto:aoconnor@bwh.harvard.edu">aoconnor@bwh.harvard.edu</a></td>
<td>Instructor</td>
</tr>
</tbody>
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Twitter Handle (if applicable)
apoboston

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- Regenerative Medicine
- Trauma
- Women's Health & Gender Biology
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Title*
Shifting Paradigm: Trauma-Informed Care

Authors*
Annie Lewis-O’Connor, Eve Rittenberg, Samara Grossman, Kiara Manosalves

PI*
Annie Lewis-O’Connor

Abstract Body (MUST be limited to 200 words, anything beyond 200 words will be truncated for print)*
Trauma, violence and abuse are deeply interconnected with poor health outcomes. Amongst adults, 30% have experienced six or more traumatic events in their lives. 1, 2 The Adverse Childhood Experience (ACE) study was a collaboration between the Centers for Disease Control and Kaiser Permanente. In a sample of 17,000 they calculated and ACE score based on childhood exposure to abuse, neglect and household dysfunction and found significant correlation between childhood exposures to violence and abuse and health outcomes in adulthood. 2 The population attributable risk for a variety of common adult health problems varies from 22.2% for asthma, to 32.5% for binge drinking to 55.7% for anxiety.3 There is incomplete knowledge and understanding of how a trauma-informed care (TIC) approach might be broadly operationalized to improve the health and the wellbeing of a population with high levels of trauma exposure. Understanding the impact of violence and trauma will help providers to respond in a helpful way, avoid re-traumatization, improve patient engagement, acknowledge resilience, and improve self-care for providers. The Partners Trauma-informed Steering committee is conducting educational trainings and developing TIC sensitive measurement tools to explore the impact on staff and patients. 1. https://www.ncbi.nlm.nih.gov/pubmed/24151000 2. http://www.cdc.gov/violenceprevention/acestudy/index.html 3. http://www.legis.state.wv.us/senate1/majority/poverty/ACEsinWashington2009BRFSSFinalReport%20-%20Crittenton.pdf

**Lay Summary (MUST be limited to 200 words, anything beyond 200 words will be truncated for print). Please keep in mind - Discover Brigham is open to the public, this lay summary needs to be appropriate for lay audiences with NO scientific background.**

Trauma, violence and abuse are deeply interconnected with poor health outcomes. Amongst adults, 30% have experienced six or more traumatic events in their lives. There is incomplete knowledge and understanding of how a trauma-informed care (TIC) approach might be broadly operationalized to improve the health and the wellbeing of a population with high levels of trauma exposure. Understanding the impact of violence and trauma will help providers to respond in a helpful way, avoid re-traumatization, improve patient engagement, acknowledge resilience, and improve self-care for providers. The Partners Trauma-informed Steering committee is conducting educational trainings and developing TIC sensitive measurement tools to explore the impact on staff and patients.

**Clinical Implications (MUST be limited to 40 words and accessible to a lay audience) - please describe the clinical implications of your research.**

The clinical implications for the partners informed-care initiative is: 1) respond to patients with trauma histories in a more meaningful way; 2) improve patient engagement; 3) Improve health outcomes; 4) lower health care costs; 5) improve staff’s self care.

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**First Name**
Huijun

**Last Name**
Liao

**Academic Degrees**
B.S.

**BWH Department**
Radiology

**BWH Division (if applicable)**
Center for Clinical Spectroscopy

**BWH ID Number**
100325821

**Email Address**
hjliao@partners.org

---

**BWH Title or HMS Rank (if relevant)**
Research Study Coordinator

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**Title**
The Effects of Tai Chi on the Brain and Muscle Measuring by MR Spectroscopy - Pilot Study

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**Authors**
Huijun Liao, Min Zhou, Lasya Sreepada, Benjamin Rowland, Han Jiang, James Balschi Alexander P. Lin

**PI**
Alexander Lin
Tai Chi, a mind-body exercise which has been shown to improve both mental and physical health. The purpose of this study was to use MR Spectroscopy (MRS) to measure the effects of Tai Chi on the brain and muscle in the elderly. Six Tai Chi naïve elderly subjects (mean age 63.6 ± 9.8, 5 females and 1 male) received a 12-weeks Tai Chi training at Greater Boston Golden Age Center (Boston, MA) with at least 2 practices per week (45 min each). All subjects were scanned with 31P leg muscle and 1H brain MRS (one exam) at Brigham and Women’s Hospital both before and after 12 weeks of Tai Chi training. Most of the subjects showed significant improved PCr recovery rate (p=0.047) and increased NAA/Cr (p=0.028) after Tai Chi training. This provided quantifiable evidences of improvement in muscle energy and beneficial neuroplasticity from Tai Chi.

Tai Chi is an ancient Chinese form exercise for mind and body. Research studies have shown that Tai Chi appears to improve thinking as well as strength in older people but have not measured a physical response. The goal of this study was to use a technology called Magnetic Resonance Spectroscopy (MRS) to measure brain and muscle chemistry to see how it can be affected by exercise such as Tai Chi. Six elderly people with no previous Tai Chi experience joined our study (their average age is 63 years old, 1 male and 5 female). They practiced Tai Chi for 12 weeks with at least 2 practices per week. We used MRS to measure their leg muscle and brain chemistry both before and after their 12 weeks of Tai Chi training. Our results showed that leg muscle energy can recover faster from a short 3-min leg-lifting exercise after 12 weeks of Tai Chi training. More importantly, we also saw an increase of a brain chemical called N-acetyl-aspartate (NAA) which is found in brain cells called neurons. This increase of NAA suggests that Tai Chi exercise may be beneficial to brain health.

Magnetic Resonance Spectroscopy is a technology that can measure how muscle and brain chemistry changes in elderly by Tai Chi exercise. Our results indicate that Tai Chi may be beneficial to muscle and brain health.