HARVARD MEDICAL SCHOOL

72ND ANNUAL

Soma Weiss
Student Research Day
January 12, 2012

Poster Sessions
1:00 - 4:00 PM
Atrium of the Tosteson Medical Education Center
260 Longwood Avenue, Boston, Massachusetts

Reception
2:00 – 4:00 PM
Atrium of the Tosteson Medical Education Center

Student Presentations and Poster Awards
4:00 – 5:00 PM
Room 209, Tosteson Medical Education Center

Welcome
Jeffrey Flier, MD, Caroline Shields Walker Professor of Medicine
Dean of the Faculty of Medicine, Harvard Medical School

Introductions
Patricia D’Amore, PhD, Professor of Ophthalmology (Pathology), Schepens Eye Research Institute
Chair, Faculty Committee for Scholarship in Medicine

Student Speakers
Nina Gold (Holmes): An integrated approach to the genetic diagnosis of mitochondrial disorders
Geon Kim (Peabody): Endothelial-to-hematopoietic cell transition in the embryo
Belinda Wang (London): Melanocyte and melanoma regulation
Shuai Xu (Peabody): Promoting medical innovation: The case of coronary artery stents

Awarding of Poster Prizes
Elizabeth D. Hay Prize for Basic Science Research
Judah Folkman Prize for Clinical / Translational Science Research
Charles Janeway Prize for International Research or Service
Robert Ebert Prize for Health Services Research or Service
Soma Weiss
1899 - 1942
The Soma Weiss Student Research Day

This day honors the memory of Soma Weiss, MD (1899-1942), an inspiring teacher and physician at HMS and an ardent supporter of student research. Soma Weiss was born January 27, 1899 in Bastercze, then a part of Hungary. He immigrated to New York in 1920 and graduated from Cornell Medical College in 1923.

Dr. Weiss came to Harvard Medical School in 1925 when he was appointed assistant at the Thorndike Memorial Laboratory and Research Fellow in the Department of Medicine. He rose rapidly, demonstrating his great ability as an investigator, teacher, administrator, and clinician. Within four years, Dr. Weiss was appointed Assistant Professor of Medicine. His medical capabilities, his diplomatic handling of difficult situations, and his amicable personality led to his appointment as Director of the Second and Fourth Medical Services at Boston City Hospital in 1932. In this position, he took charge of the fourth year medical students, winning their admiration and affection. One of the important contributions he made to teaching was in his development of the Clinico-Pathological Conference at the City Hospital. His own bi-weekly Pharmacological-Therapeutic Conference gave the students unusual insight into the use of drugs.

Soma Weiss possessed all the qualifications necessary for the great clinician. He was a master of observation. His ward rounds were excellent; while conducting them, he never neglected the patients, the students, or the visiting physicians. He kept them all in proper balance while he dominated the whole. He wisely insisted that clinical work must be the basis for the study of disease.

In 1939, Soma Weiss became the second Physician-in-chief of the Peter Bent Brigham Hospital. He died January 31, 1942 from the rupture of a congenital intracranial aneurysm. In the intervening years, his generous spirit, his eager and able services for the Hospital, his great abilities as a physician, investigator, and teacher, left an indelible imprint on the many students he mentored.

Harvard Medical School wishes to thank the Weiss family for their support of the annual Soma Weiss Student Research Day.
Faculty Committee for Scholarship in Medicine

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John Ayanian, MD
Raymond Chung, MD
Jennifer Haas, MD, MSPH
Richard Mitchell, MD, PhD
Janet Mullington, PhD
Shiv Pillai, MD, PhD
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Gordon Strewler, MD

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Outcomes Research, Quality
Improvement, and Clinical
Epidemiology
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Health Care Policy and Health
Services
Lisa Iezzoni, MD, Chair

Medical Humanities
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Global and Community Health (including Advisory Committee on
Systems Innovation)
Co-Chairs:
Barbara Gottlieb, MD, MPH
Felicia Knaul, PhD
Rushika Fernandopulle, MD, MPP
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A Locus on Chromosome 11 Regulates Synchondrosis Fusion in DBA/2J Mice

Allysa C. Adams
Harvard School of Dental Medicine, Oliver Wendell Holmes Society, Class of 2014

Mathew L. Warman, MD
Orthopaedic Research Laboratories, Children’s Hospital Boston
Department of Genetics, Harvard Medical School

Cranial base growth plates are important centers of longitudinal growth in the skull and are responsible for the proper anterior placement of the face and the stimulation of normal vault development. Structurally, synchondroses in both humans and mice are arranged as two bilaterally symmetric growth-plates, each containing four regions of chondrocytes at specific developmental and morphologically distinguishable stages: the resting zone, the proliferative zone, the pre-hypertrophic zone, and the hypertrophic zone. The progression of chondrocytes through these zones is a tightly regulated process dependent on both systemic and local mediators. Here, we report that the presphenoidal synchondrosis (PSS), a midline growth plate of the murine cranial base, closes in DBA/2J mice but not in other common inbred mouse strains. Closure in the DBA/2J strain is preceded by a loss of growth plate organization and the formation of a cartilaginous protrusion, which we have documented in a histological series. We investigated the genetic architecture of PSS closure by crossing DBA/2J mice with C57BL/6J and DBA/1J mice whose PSS remains open throughout development and then examining the F1, F1 backcross, and F2 intercross offspring for PSS closure. To map loci which contribute to PSS closure, we genotyped offspring with genome-wide SNP arrays. We observed that PSS closure does not follow a simple pattern of inheritance, but in the DBA/2J x C57BL/6J cross a locus that strongly influences this trait is detectable on chromosome 11.
Bacteremia Detection Using Aqueous Multi-Phase Polymer Systems

Phillip C. Aguilar
Harvard Medical School, Walter Bradford Cannon Society, Class of 2014

George M. Whitesides, PhD
Woodford L. and Ann A. Flowers University Professor
Department of Chemistry and Chemical Biology, Harvard University

Bacteremia accounts for 30-40% of all cases of severe sepsis and septic shock and causes significant morbidity and mortality both in the US and worldwide. Blood culture is the current gold standard for diagnosing bacteremia and requires minimally 2-3 days for results to become available. Even with newer techniques that attempt to shorten the diagnosis time, such as hybridization and amplification assays or detection of serum biomarkers, precious time is lost during which progression to sepsis could be prevented by treatment with targeted antibiotics. Thus, a gap exists for a technology to provide a fast, inexpensive diagnostic with positive predictive ability for bacteremia that can be used directly on whole blood specimens.

This study examined the density of erythrocytes and *E. coli* to determine if a difference existed that could be identifiably resolved and visualized using aqueous multi-phase polymer systems (AMPS). We hypothesized that a higher density of *E. coli* would allow for physical separation from erythrocytes and visualization using AMPS. We tested this hypothesis by developing an aqueous single-phase polymer system (ASPS) of Ficoll to determine the density of RFP-expressing *E. coli* using a sink-or-float threshold visualized by fluorescence scan. Once a density step was identified that facilitated the selective separation of *E. coli* from erythrocytes, we developed an AMPS of Ficoll/PEG, characterized by physiological pH and osmolality, to physically separate erythrocytes from both RFP-expressing *E. coli* and a BL-21 *E. coli* strain. The BL-21 *E. coli* were visualized using crystal violet dye and a serial dilution was performed to determine the lowest concentration of the *E. coli* in blood visible after separation.

Preliminary data suggest that AMPS can successfully separate RFP-expressing *E. coli* from erythrocytes both by visual inspection and by fluorescence scan and that it can separate a BL21 *E. coli* strain from erythrocytes visualized with crystal violet dye at clinically relevant concentrations of *E. coli* in blood. However, data analysis is ongoing to confirm these initial findings. If confirmed, these results would demonstrate that AMPS provides a technology that is capable of detecting clinically relevant concentrations of bacteremia and improving the time and cost of bacteremia diagnosis compared to the gold standard of blood culture.
Autoproteolysis of *Clostridium difficile* Toxin B

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*Clostridium difficile* is the leading cause of hospital-acquired diarrhea in the United States, Canada, and many European countries. This disease often results in patients who have been treated with antibiotics or chemotherapeutics, which presumably disrupt normal intestinal flora, thus enabling *C. difficile* to colonize the colon. Upon colonization, *C. difficile* releases two large protein toxins, Toxin A and Toxin B, which damage the intestines and trigger a large inflammatory response in patients. This disease can even be life threatening in some patients.

It is known that *C. difficile* Toxin B inactivates Rho-GTPases leading to disorganization of the actin cytoskeleton, which causes cells to appear rounded under microscopy. Although the precise mechanism of toxin uptake into a cell is unclear, evidence suggests it is a four step process that includes autoproteolysis of the toxin. There is controversy over the issue of toxin processing and disease, but many believe that the toxin must be cleaved in order to see rounding of the intoxicated cells.

We therefore hypothesized that evidence of processed Toxin B must be present in rounded, toxin exposed cells. To test this hypothesis, we treated CHO cells with Toxin B of the historical or the hypervirulent strain of *C. difficile* and observed to see when the cells began rounding. Once cells were rounded, they were washed and then lysed. The lysates were then analyzed to confirm the presence of cleaved Toxin B by using an antibody to the C-terminal region of the toxin.

Initially, we did not see evidence of processed toxin. Western blots of cell lysates showed a single band that was the size of the full length toxin. After trying multiple methods of lysing and fractionating the cells, we did see evidence of toxin processing. This discovery was particularly interesting because we saw the smaller C-terminal region of the toxin in the mitochondrial fraction, a finding which has not been seen before.

We concluded that the toxin is cleaved in order to result in rounding of intoxicated cells. We also believe that our discovery of the C-terminal region of the toxin in the mitochondrial fraction provides additional information on the mechanism of toxin processing and will facilitate more research on the subject. This information could be helpful to others who are currently researching *C. difficile* Toxin B.
GP Practice Presentation and Referral Rates for Benign Gynecological Conditions

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Background: Referrals to secondary care are a significant source of costs for the England National Health Service (NHS). In an effort to reduce these costs University College of London (UCL) Partners and Whittington Health have been working on models to reduce referrals to secondary care while simultaneously improving the quality of care for patients. One area of interest is within Women’s Health, in particular benign gynecological referrals. This is an area where the utilization of community care pathways could reduce the number of referrals to secondary care, while simultaneously increasing the quality of care delivered.

Objective: To gain a snapshot of the presenting benign gynecological conditions for General Practitioner (GP) practices in Haringey (Northern London), a borough which refers to the Whittington Hospital. To determine the referral rates for the major presenting benign gynecological conditions in GP practices in Haringey.

Methods: The EMIS LV health records of 4 Haringey practices were queried for patients who had a visit within the past five years, coded for the following conditions: micturition infrequency; micturition control; micturition stream; genitourinary pain; fertility problem; cervical vaginal and vulval inflammatory; genital tract disorder; pruritus vulvae; vulval irritation; incontinence or urine; and incontinent of faeces. An output report was then created from these patients was created with the following fields: patient id; sex; postcode; age; referrals and dates; medications and dates; bmi, urinalysis, gynecological diagnoses and dates, and co-morbid diagnoses and date. Referrals were matched with conditions by pairing any visit for a condition with any referral that occurred within 14 days. These were the only referrals that were counted and compared.

Results: A total of 6891 visits were examined across the four practices. The majority of presenting conditions at each practice were for urinary incontinence and menstrual issues. Referral rates and proportions varied at each practice, however at all practices urinary incontinence and menstrual issues made up a large proportion of all referrals.

Conclusion: An intervention to reduce benign gynecological referrals from GPs to secondary care should focus on urinary incontinence and menstrual issues to maximize impact.
WHO Surgical Safety Checklist Modification Globally:
Process Checks Proliferate, Communication Components Disappear

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Intro: Since 2008, the WHO checklist has been adopted by over 4000 hospitals globally. The WHO has encouraged checklist modification. This study examined a diverse sample of checklists in order to assess patterns in checklist modification around the world.

Methods: 113 checklists were studied, representing 37 countries and 19 US states. Checklists were analyzed for total item number and the nature of original WHO items dropped and new items added. Items were categorized according to whether they accounted for completion of a process or promoted communication within the surgical team.

Results: Extensive modification of the original WHO checklist was observed. Checklists studied had more items on average than the original WHO checklist (33.0, SD=8.2 vs. 27), and contained an average of 23.4 (SD=3.5) of the 27 original WHO checklist items. US checklists added more new items (average total item number was 34.9 vs. 31.4, p = 0.0721) and maintained fewer original items (21.7 vs. 24.2, p = 0.0003) than did non-US checklists. The WHO checklist has 6 communication items; the average US checklist contained 4.23 of these items, while the average non-US checklist contained 5.23 (p= 0.0017). US checklists had significantly lower frequencies of items promoting discussion of anticipated critical events and anticipated blood loss by the surgeon, sharing of anesthetist concerns, and review of key aspects of patient recovery by the team.

Discussion: As encouraged, the checklist is widely modified, but certain aspects of modification patterns raise concerns. The high frequency with which communication items were removed is alarming, as many studies have demonstrated significant room for improvement in communication among members of the surgical team, and that improvements in operating room communication lead to a reduction in errors and better patient outcomes. Checklists appear to grow in length on average: the ideal length for a surgical checklist is unknown, but checklists that are long and complex may be too cumbersome to be used effectively. On average, US checklists are longer than non-US checklists and eliminate more WHO communication items; this modification pattern may be due to differences in national health care structures and local surgical cultures.
Early postnatal Lipoxin A4 levels are increased in preterm infants who develop chronic lung disease

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Polyunsaturated fatty acids (PUFAs) such as Docosahexaenoic Acid (DHA) and Arachidonic Acid (AA) are important in fetal and infant neurodevelopment, development of immunity, and regulation of inflammation. Since the neonatal cytokine balance is skewed towards inflammation, proinflammatory conditions account for a large percentage of morbidity in the neonatal intensive care unit (NICU). This is particularly important in premature infants who are at risk of inadequate accrual of these fatty acids due to cessation of placental transfer caused by premature birth.

Previously, the Martin-Freedman lab demonstrated significant alterations within the first postnatal week in blood PUFA levels in preterm infants from levels measured at birth. They have also shown an association between lower PUFA levels and inflammatory diseases such as chronic lung disease (CLD) and nosocomial sepsis.

Based on these prior findings, we hypothesized that decreased levels of DHA and AA increase the risk of CLD by leading to reduced levels of fatty acid derived molecules involved in terminating inflammation, namely lipoxin A4 (LXA4), a lipid mediator derived from AA that has been found to have both anti-inflammatory and pro-resolution effects.

To test this hypothesis, we quantified by enzyme-linked immunosorbent assay (ELISA) the amount of LXA4 in the serum of 4 preterm infants with CLD at day of life (DOL) 0, 7, and 14 and compared these results with those of 4 preterm infants without CLD.

We observed that infants with CLD had higher LXA4 levels compared to infants without CLD throughout the first two postnatal weeks. Infants with CLD demonstrated mean serum LXA4 levels of 0.403 ng/ml, 0.470 ng/ml, and 0.425 ng/ml on DOL 0, 7, and 14, respectively; whereas, serum LXA4 levels in infants without CLD were 0.288 ng/ml, 0.263 ng/ml, and 0.222 ng/ml respectively at each time point.

In contrast to what was originally hypothesized, infants who later developed CLD appeared to appropriately increase their production of LXA4 levels in response to the increased inflammatory environment compared to infants without CLD. However, the fact that these infants still developed disease despite this appropriate immune response raises further questions in the immunocompetency of the preterm infant and additional pathways to explore in and role of fatty acids in regulating inflammation.
The Determinants and Mechanism of B-ALL Entry to the Central Nervous System

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Acute lymphoblastic leukemia (ALL) is a malignancy of the adaptive immune system that affects B or T cells. While the treatment of ALL has been an overall success, a number of significant challenges remain. Notably, both B- and T-cell ALL exhibit significant tropism for the central nervous system (CNS), which necessitates the administration of prophylactic cranial irradiation or intrathecal chemotherapy to most ALL patients; both of these carry significant long- and short-term risks. Surprisingly, little is known about the mechanisms by which B-cell ALL (B-ALL) is able to gain access to the CNS. We used a mouse model of B-ALL to explore in vivo whether knockdown of chemokine receptors and cell adhesion molecules implicated in non-malignant B-cell entry to the CNS is able to slow or block B-ALL entry to the CNS, and we found a putative role for the chemokine receptor CXCR4. We also performed histology and X-ray computed tomography studies in this model, which implicate osteolytic destruction of the skull by leukemic cells in the entry of B-ALL to the CNS. Finally, we propose drug induced increases in B-ALL migration to the CXCR4 ligand SDF-1α as a possible contributor to CNS relapse after treatment with the BCR-Abl inhibitor Dasatinib.
Rate of Shunt Failure after ETV and ETV-CPC Treatment for Hydrocephalus in Rural Uganda

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Though neurosurgery is not traditionally associated with global health interventions, the need for neurosurgical expertise is dire, especially in East Africa where there is about 1 neurosurgeon per 10 million people compared to the United States’ ratio of 1 neurosurgeon per 62,500 people. This health inequality is bolstered by an estimated 100,000 new cases per year of infant hydrocephalus in sub-Saharan Africa. However, even if neurosurgeons practice in the developing world, treatments may not be tailored to the correct context—hydrocephalus treatments call for expensive shunts that require follow-up care due to shunt failure. Consequence of poverty, lack of health infrastructure and technology, poor transportation, and lack of training opportunities, neurosurgery does not have a strong foothold in developing nations.

Though incorporating neurosurgery in developing nations is challenging, it is surmountable, as demonstrated by academic centers and organizations, such as CURE Children’s Hospital of Uganda (CCHU). Studies from CCHU have shown that alternative treatments for hydrocephalus, specifically endoscopic third ventriculostomy (ETV) and endoscopic third ventriculostomy with choroid plexus cauterization (ETV-CPC), were sustainable, effective treatments. However, a subset of patients receiving either ETV (±CPC) treatment requires post-procedural shunt placement if this treatment fails. The effect of prior ETV (±CPC) on subsequent shunt survival has not previously been investigated.

The current study investigates the time to shunt failure in patients who received upfront shunts, had initially successful ETV (±CPC) followed by shunts, or had initially abandoned endoscopy followed by shunts. We hypothesized that patients with initially successful ETV (±CPC) procedures prior to shunt placement would have lower rates of shunt failure. To test this hypothesis, we designed a retrospective cohort study including 1476 patients using CCHU’s prospectively collected clinical and demographic patient data.

In patients that had a successful ETV (±CPC) that later failed, the adjusted hazard ratio, accounting for age at shunt placement and etiology of hydrocephalus, was 0.74 (CI [0.56-0.98]; p<0.035). Conversely, patients that had shunt placement during an abandoned endoscopy had an adjusted hazard ratio of 1.34 (CI [1.06-1.69]; p=0.14). Thus, patients with a previously completed ETV (±CPC) had a lower risk of subsequent shunt malfunction over time suggesting a secondary benefit from primary endoscopic treatment even in the context of treatment failure.

These results can have major impacts on developing sustainable, more appropriate solutions for resource-poor settings in the context of hydrocephalus, and will inform best-practices.
In vitro identification and characterization of c-kit+ murine lung stem cells

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Cell-based therapy is a potentially novel approach for the treatment of devastating, typically incurable chronic pulmonary diseases (including pulmonary hypertension and chronic obstructive pulmonary disease) – the only major disease category increasing in prevalence and a leading cause of worldwide mortality. However, significant controversy exists regarding the nature and existence of an endogenous lung stem cell. By definition, a stem cell must have the capacity for self-renewal, clonogenicity, and multipotency. In the lung, several cells with combinations of the above traits have been previously identified in different anatomical lung regions, but none is unambiguously a stem cell.

Our laboratory has previously shown the existence of a c-kit+ human lung stem cell (hLSC) that is able to make human alveoli, bronchioles, and pulmonary vessels in vivo (in press). This cell could be critical for lung homeostasis and tissue regeneration after injury. We now propose to extend this finding to the mouse lung: given the wealth of murine models of pulmonary disease and the molecular biology techniques possible in mice, discovery of a c-kit+ murine lung stem cell (mLSC) would have tremendous implication for preclinical studies on developing cell-based regenerative therapy. Hence, we hypothesize the existence of a c-kit+ lung stem cell in the mouse lung that will be self-renewing, clonogenic, and multipotent.

We have developed a standard protocol for the isolation of putative mLSCs that are c-kit+/lineage- (by extension CD45-). Several samples (n=3) of these cells have been analyzed by FACS. In general, these cells have very low expression of markers of epithelial, endothelial, smooth muscle, hematopoietic, or mesenchymal lineage confirming that these cells are likely stem/progenitor cells. However, these cells do not appear to express NANOG, OCT4, SOX2, or KLF4 raising doubt as to their pluripotency. Two clones have been generated following FACS sorting and these were ckit+, but require further study. At pro-differentiation doses of AZA, these cells appeared to differentiate into epithelial cells.

In summary, we have characterized the putative mLSCs by FACS, shown that they are self-renewal and clonogenic and limited samples, and are in the process of confirming expression via qRT-PCR. Ultimately, this study is a stepping stone to in vivo experiments needed to definitively prove that our target cell is a true stem cell that can be used for regenerative cell therapy.
Imaging the tumor microvascular environment using optical frequency domain imaging

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Angiogenesis, the sprouting of new blood vessels from existing ones, is a critical step in the development of a tumor. Using Optical Frequency Domain Imaging (OFDI), an imaging modality particularly good at imaging microvasculature over large areas, we monitored angiogenesis of renal cell carcinoma tumor. Following recovery from a surgery to create a dorsal skinfold chamber, a tumor spheroid was implanted. Mice were then imaged immediately following the injury as well as every day for approximately two weeks. The images captured by OFDI showed tumor vascularization with characteristic abnormalities in vessel density, size, and tortuosity. These results demonstrate that OFDI is an excellent modality to longitudinally image tumor angiogenesis in vivo.
The Role of Insulin of Bone Growth, and the Relation to DeltaFosB/AP1

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Arthritis and Osteoporosis are debilitating chronic disorders that cost billions of dollars in health care expenses, and cause an unquantifiable amount of pain and suffering worldwide. With few exceptions, therapeutic targets to aid in these disorders have historically been elusive. In recent years there has been an intense search for bone anabolic targets. One of these is DeltaFos B, a transcription factor that has been shown to increase bone formation postnatally.

Delta FosB is a natural splice variant of Fosb, a member of the AP1 family of transcription factors. Being truncated, it acts as an antagonist to FosB activity. Dr Baron’s lab has demonstrated that one of the mechanisms by which DeltaFosB affects bone metabolism is through increasing energy expenditure and insulin sensitivity. However, the exact mechanisms and pathways behind DeltaFosB’s actions are not well understood. One hypothesis is the synergetic role of the Insulin/AKT pathway, and its contribution to anabolic processes. Consequently, the relation of AP1 activity and the Insulin/AKT pathway were examined.

To assess and quantify the relations of AP1 transcriptional activity and insulin signaling required both in-vivo and in-vitro experiments. The initial experiments involved transfection of different DNA constructs to overexpress or repress AP1 activity, using C2C12 cells induced in the osteoblast lineage. Following the transfection, the cells were stimulated using known insulin/AKT agonists, and responses quantified via western blot analysis. Pilot experiments showed a potential correlation between insulin signaling and AP1 expression.

The experiments were then repeated in 96 well plates, and quantified in a series of insulin target gene luciferase assays to examine their transcriptional activity in the presence of FosB or DeltaFosB.

To coincide with the in vitro studies, wildtype and DeltaFosB transgenic mice were stimulated with insulin. Various tissues, including the hypothalamus, liver, and skeletal muscle were removed post-mortem. Tissue lysates were created, and quantified for insulin signaling activity via western blot analysis.

Through these experiments, it appears that there may be a correlation between AP1 activity and activation/repression of the Insulin/AKT pathway. Further, certain organ systems may play a larger role than others. Experiments will be continued, but crucial links between the two pathways show promise.
Exosomes are 30-100nm extracellular vesicles released by exocytosis following the fusion of multivesicular endosomes with the plasma membrane. These vesicles are commonly found in biofluids, including blood, urine, synovial fluid, cerebral spinal fluid, and saliva. Physiological roles of exosomes include expulsion and exchange of cellular material, and intercellular communication via proteins, mRNAs, and miRNAs. While exosomes are released in all proliferating cell types, the rate of release is enhanced by pathological conditions such as inflammation and cancer. Enhanced knowledge of exosome output and contents in healthy vs. disease states may provide tools for earlier diagnosis of disease, including the discovery of disease-specific biomarkers contained within the exosomes and monitoring therapeutic protocols. We hypothesized that biofluids from patients in a disease state would contain more exosomes than biofluids from healthy patients. A secondary aim of the study was to compare the effectiveness of different exosome extraction methods.

To perform the study, exosomes were extracted from three biofluids: healthy saliva, healthy synovial fluid, and synovial fluid from patients with osteoarthritis (OA). Two extraction methods were performed for the comparison: ultracentrifugation (gold-standard) and ExoQuick™ polymer-based exosome precipitation solution. Extracted exosomes were examined by TEM and quantitated using NanoSight’s Nanoparticle Tracking Analysis. RNA was extracted from the exosomes using Trizol and the mRNA concentration and quality were measured using the NanoDrop and Agilent’s Bioanalyzer.

The average exosome concentration in OA synovial fluid following ExoQuick™ was 3.45x10^10 exosomes/mL compared to 2.91x10^10 exosomes/mL in healthy synovial fluid, a difference of 18.6%. When isolated by ultracentrifuge, the average exosome concentration in OA synovial fluid was 1.44x10^10 exosomes/mL compared to 1.18x10^10 exosomes/mL in healthy synovial fluid, a difference of 22%. The average increase in exosomes extracted from all synovial fluids by ExoQuick™ was 144% more than by ultracentrifugation. Average exosome concentration from healthy saliva was 7.54x10^9 exosomes/mL by ExoQuick™ and 6.99x10^9 exosomes/mL by ultracentrifugation, a difference of 7%. RNA of moderate quality was extracted from exosomes of all three biofluids.

The results of our study demonstrated that biofluid from a diseased state like OA contain more exosomes than from a non-disease state. Additionally, it was shown that ExoQuick™ is more effective at isolating exosomes than ultracentrifugation. The exosome analysis of disease-state saliva, such as from patients with oral squamous cell carcinoma, will be performed in the future and is expected to strengthen our hypothesis. The findings provide the basis for the potential discovery of exosome-derived diagnostic tools.
The Village Health Worker Model: A Strategy for Improving Drug Delivery Access and Overcoming Malnutrition in Mirriah Region of Niger

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Millennium Development Goal 4 aims to achieve a two thirds reduction in child mortality by 2015. Currently, the major causes of under-5 (U5) mortality in Africa are neonatal-related, malaria, diarrhoea and pneumonia; malnutrition plays a complex cause-effect role in these pathologies, and is associated with up to half of all deaths. The majority of these children die without being seen by any health professional. One tactic to target this issue is the decentralization of health care through the training of village workers. These community health workers (CHWs) recognize and manage most-prevalent diseases, and educate their communities in healthy living practices. This intervention gives health care contact to children who would otherwise have no access to care, and attempts to fill the gap caused by a vast lack of health care professionals.

Niger was ranked 167/169 in the 2010 United Nations Human Development Index. In 2008, the U5 mortality rate was 167/1000 live births. ALIMA (The Alliance for International Medical Action) is a non-governmental organization (NGO) which, with a local Nigerien NGO, has set in place decentralized interventions targeting U5 malnutrition in the Mirriah region in Niger. This region has consistently had amongst the highest rates of severe acute malnutrition recorded in Niger. ALIMA intends to expand the range of interventions targeting U5 mortality and to decentralize health interventions to village level. This is easier said than done: unlike many areas where the CHW strategy has been implemented, Niger has a dispersed population, and is clouded by a complex sociopolitical environment with frequent terrorist attacks. Careful consideration of existing CHW models was required in order to make an educated decision about cost-effective interventions to be implemented in Niger.

The goal of my summer project was to research the expansion of the existing CHW malnutrition programme to include sustainable interventions that will have the highest impact on U5 mortality in Niger. Research methodology involved synthesis and analysis of the existing literature, field interviews with heads of mission, and conferences with ALIMA programme managers. Research conclusions incorporated practical suggestions on the ideal structure for the CHW model, including number of CHWs per U5, number of tasks which can be managed by a CHW, the use of facilitated referral systems, training of CHWs, ensuring staff retention of CHW volunteers, and effective scaling-up strategies. A practical three-year implementation timeline was recommended, and parallel research imperatives were suggested to allow further studying of effective decentralization models.
Identifying the region of BRCA1 that interacts with RFC/Rad17/Rad9 complexes to repair stalled replication forks

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Women with BRCA1 gene mutation experience a 65-85% risk of developing breast or ovarian cancer, as compared to a 12% risk in the general population. While many mutations lead to expression of a truncated protein, the BRCA1 gene is also dotted with non-truncating missense sequence changes of unknown significance. We are trying to understand whether certain mutations of this type are clinically important and, if so, why.

The BRCA1 protein is best known for its role in double strand break repair. Recent work in our laboratory has shown that BRCA1 is also involved in the cellular response to bulky adduct DNA damage, and, in particular, in the resolution of stalled replication forks. This repair pathway is of possible clinical interest, because it is activated after damage caused by naturally-occurring small molecules, such as reactive estrogen metabolites that are known carcinogens. Similarly, BRCA1 breast cancer depends upon the puberal and post-puberal secretion of estrogen. Thus, one wonders whether a breakdown in the response to bulky adduct-driven replication fork stalling contributes to BRCA1 breast cancer development.

A specific set of interactions of BRCA1 with the RFC/Rad17 and Rad9-Hus1-Rad1 complexes are required for efficient resolution of bulky adduct-generated stalled forks. Thus, we asked whether a specific region of BRCA1 participates in these interactions and identified two, distinct, ~300 aa BRCA1 regions (fragments 3 and 5) that functioned in this regard in cell-free assays. Fragment 3 (aa502-802) bound Rfc1 and Rad9, while fragment 5 (aa1005-1313) bound Rad17. Further characterization of fragment 3 showed that its N-terminal region (aa502-650) was sufficient for the interaction with Rfc1 and Rad9. We asked whether any of the missense sequence changes in the regions encoding fragment 3, which exist in women whose germ line BRCA1 gene was previously sequenced, result in loss of the interaction between BRCA1 and Rad9/RFC. Introduction of the E597K change into fragment 3 decreased the efficiency of its binding to Rad9. E597K is predicted to disrupt BRCA1 tertiary structure. Introduction of other known missense changes in this region (M658I and R504H) did not grossly disrupt this interaction.

Our results suggest that distinct regions of BRCA1 participate in specific interactions with Rfc1, Rad9, and Rad17 at stalled replication forks after bulky adduct DNA damage. The question is whether a defect in this process in women with certain germ line BRCA1 mutations triggers chronic replication stress and genomic instability and, thereby, contributes to breast tumorigenesis.

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Increasing ethnic diversity amongst patient populations has created challenges for health care providers to communicate and deliver care. In 2010, a published review of health care disparities with regard to Arab-Americans concluded, “The relationship between Middle Eastern patients and populations of Arab origin with western health care professionals are by no means free of cultural misunderstandings. The relationship is often strained by mutual cultural misunderstanding as well as communicative and linguistic hardship.” This disparity in delivery of care is related to both language and cultural barriers. In the larger urban hospital setting, interpreters serve as cultural brokers and aid the doctor and patient in their communication. However, outside of major medical centers, they are not always present to help the physician or dentist communicate with the patient and family. In the clinic, the relative absence of cultural brokers and resultant miscommunication acutely translates into disparities.

The aim of this investigation is to explore the sensitivities of communication with Arabic-speaking patients and design a publishable resource that assists health care professionals – physicians, dentists, and nurses – with their delivery of care.

Coming from twenty-one Arab countries, diverse within their own national boundaries, immigrants and subsequent generations demand a heightened cultural competence on the part of their caregivers. Materials that will help health professionals in the clinic with Arabic-speaking patients need to integrate language, socioeconomics, culture, gender, literacy levels, and religion as fluidly as possible.

The investigation will be based on the experiences of health care professionals and Arabic-speaking residents in the Boston area. The preliminary round of interviews will be to broadly understand the challenges of Arabic non-Arabic speaking professionals using the semi-structured format. This will refine my objectives in the second stage, which will aim to identify the most frequently asked questions and the specific sensitivities and variations within each one. I will script dialogues situated in the clinic. These dialogues will then be shared with doctors interviewed previously as well as others to gauge their effectiveness as cognitive walkthroughs.

I am working on stage two currently and am not in a position to report results.
Searching for Rare Bacterial Phyla in the Human Oral Microbiome

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It is estimated that a healthy adult harbors ten times as many microbial cells as human cells. It is still yet to be fully understood what roles these microorganisms play in development, physiology, immunity and nutrition. In order to understand the complex roles microorganisms have in these processes, it is essential to first characterize and classify the microorganisms that make up the human microbiome. Our research focused on the human oral microbiome in particular.

It is estimated that only approximately 40% of bacteria in the human oral cavity are currently cultivable. Because of this, the best current methodology for characterizing the oral microbiota is the culture-independent technique of identifying bacteria by their 16S rRNA sequences. In this method, DNA is first isolated from multiple surfaces in the oral cavity (teeth, gingival sulcus, tongue, cheeks, hard and soft palates, and tonsils). Subsequently, degenerate primers are designed which will selectively amplify 16S rRNA gene fragments. The amplicons are then cloned into Escherichia coli. The 16S rRNA gene inserts are sequenced and the information is used to identify new taxa or collect data on the relative abundance of known taxa.

This method typically relies on using a “universal” primer set designed to amplify 16S rRNA fragments from a wide range of bacteria. Our research focused on using primer sets designed to be more specific for five rare phyla: Chlorobi, Chloroflexi, GN02, WPS-2 and SR1.

Our data show that the presence of Chloroflexi, GN02 and SR1 can be detected in the human oral cavity using more specifically designed primers. Our data also shows that the “universal” primer set commonly used to characterize microbiomes by 16S rRNA screening select against these phyla, causing them to be under represented or missed.
Embedding Endothelial Cells in Acellular Bone Matrices

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Endothelial cells (ECs) are dynamic with a phenotype that is dictated by microenvironment. In their quiescent (non-dividing) state, they impose a semipermeable barrier that carefully regulates thrombosis, leukocyte adhesion, etc. In the face of controlled injury, ECs attain a reparative phenotype that stimulates healing, but if overwhelmed, ECs can become dysfunctional promoting inflammation, coagulation and unbridled proliferation. The initiation and perpetuation of atherosclerosis is in large part determined by the balance of EC quiescence, activation and dysfunction. Tissue engineered constructs allow ECs to be retained in a single state relatively immune from further environmental forces. ECs seeded in 3D matrices, such as collagen-based matrices, secrete anti-proliferative, anti-thrombotic, and anti-inflammatory agents that promote vascular repair.

The architecture of the 3D matrices resembles strongly the architecture of the bone marrow. ECs within the bone marrow tend to aggregate along bone spicules and fatty globules, suggesting that the benefit of EC-embedding within 3D matrices arises because synthetic matrices recapitulate marrow architecture and that the bone marrow architecture creates a privileged niche for ECs. The hypothesis of this study was that bone marrow architecture confers an EC phenotype distinct from ECs in 2D tissue culture plates, a state that significantly promotes vascular repair.

Rat tibiae and femora were harvested, cut into segments, and decellularized. Acellular bone segments (n = 8), average diameter of 6.0 ± 1.2 mm and thickness of 2.5 ± 0.5 mm, were seeded with human umbilical endothelial cells (HUVEC). The first group (n = 3) was incubated overnight in 4 x 10⁶ HUVECs labeled with PKH26 dye and a second group (n = 3) was incubated in 4 x 10⁶ HUVECs without dye. Cell-seeded bone segments were trypsinized and 1.9 x 10⁵ ± 5.7 x 10⁴ cells were recovered and detected by Coulter cell counting as compared to 31 ± 1.4 detected cells in control samples incubated in media. Trypan blue exclusion of bone segments seeded with PKH26-labeled HUVECs showed an average cell viability ratio of 3.6:1; however, fluorescence microscopy of PKH26-labeled HUVECs was inconclusive due to autofluorescence from the bone segments.

These findings suggest that ECs can be viably seeded onto acellular bone matrices. Future studies will further discriminate ECs with immunostaining for EC specific markers such as VE-cadherin and use RT-PCR to analyze changes in gene expression.
The Status of Oral Health and Oral Health Literacy in the Nursing Home Population

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During the summer of 2011 I worked with Dr. Taru Kinnunen on several projects assessing the oral health status of nursing home residents in the United States. I participated in the Oral Cancer Screening Study, a project that was already in progress and in which Dr. Kinnunen was the Principal Investigator. The aims of this study were to administer a questionnaire and an oral exam to nursing home residents to identify risk factors for oral cancer, screen for oral cancer, and set up a follow-up visit and treatment plan if any oral cancerous or pre-cancerous lesions were noted. I assisted in adding new data to the existing database and will be analyzing a subset of the data in a secondary analysis to determine the relationship between the number of missing teeth and years of lifetime tobacco use in this population.

In addition, Dr. Kinnunen and I co-authored a presentation titled Tobacco Use Practices and Policies in United States Nursing Homes that was presented at the International Society for the Prevention of Tobacco Induced Disease in Vienna in September 2011. I was a lead researcher for this presentation in which we described the government policy mandating that nursing homes allow residents to smoke if they receive Medicare/Medicaid reimbursement, that smoking poses an increased risk to elderly smokers and fellow residents, that smoking is responsible for a significant amount of fire-related incidents in nursing homes, and that available cessation programs are not tailored to the specific needs of seniors. We recommended altering these policies and called for additional research to determine the type of cessation program most effective for nursing home residents.

Finally, Dr. Kinnunen's research team and I surveyed the existing literature on oral health literacy in nursing home residents and staff. We concluded that oral health literacy is low among both residents and care providers. We intend to write a literature review on this topic that will include recommendations for future trials to determine the most effective way to improve oral health literacy in the nursing home population in order to increase the oral health of the elderly and the oral care they receive.
Relating Living Arrangements to Concern with Facial and Body Morphology

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The objective of this project was to compare the influence of boarding at school on concerns with appearance of the orofacial area (OFA) and body shape in two Catholic all-girls schools in Taiwan. The questionnaires contained 59 exploratory OFA items which were added to 33 of the already-validated Cooper et al. Body Shape Questionnaire (BSQ), then translated into Chinese and back-translated into English for verification that the English and Chinese version meant the same thing. Following IRB approval by Harvard and the equivalent in Taiwan, the questionnaires were distributed to 11-12 graders; of which 175 valid responses were returned from boarding students (B) and 486 valid responses from those living at home (H).

Results: Except for Bs being significantly taller than Hs (p<.001), there were no other demographic differences: age (yrs): B 16.6 ± 0.6, H 16.6 ± 0.6; weight (lbs): B 113.2 ± 13.1, H 112.3 ± 18.2; height (in) B 63.5 ± 2.0, H 62.6 ± 2.1; BMI B 19.8 ± 2.2, H 20.1 ± 3.0.

Total OFA scores for Bs 112.1 ± 25.6 were not significantly different from Hs 111.3 ± 28.4; for BSQ, however, the total B score of 89.8 ± 30.15 was significantly or near significantly higher than the Hs with 84.4 ± 33.8 at p<.013. The total BSQ for both Bs and Hs was significantly higher than normative score of 71.9 ± 23.6 at p<.001 and lower than 129.3 ± 17.0 for probable bulimics at p<.001. OFA / BSQ correlated significantly for H (r=0.69 at p<.001) and B (r=0.55 at p<.001), at p<.097.

Although total OFA scores for B and H were not significantly different from each other, there were seven out of 59 or 11.9% which were significant or near significantly greater concerns at p<.06 for B than H, the number of which was not greater than chance. For the BSQ, however, ten out of 33 or 31.2% of the B items were significantly different from H, which was greater than chance.

In addition to the influence of greater B than H opportunities for self and peer evaluation, the differences between Bs and Hs may be a function of greater supervised study requirements and academic expectations with less dietary freedom than Hs who have greater access than Bs to comfort food and commercial skin, hair, and eye products.

Conclusion: Whatever differences exist between B and H in distribution and magnitude of OFA and BSQ concerns may be related to psychosocial/behavioral and institutional factors.
Patient Experience in Safety-Net Hospitals:
Implications for improving care and value-based purchasing

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When patients have poor experiences with the healthcare system, they are less likely to recover fully and quickly from their illness and less likely to be adherent to their treatment regiments. Therefore, suboptimal patient experience has important health consequences for patients and financial consequences for the healthcare system at large. Optimizing patient experience is particularly important among safety-net hospitals (SNHs), which provide an essential service in caring for vulnerable populations, including Medicaid patients, the uninsured, and the underinsured. In this study, we focused on the ability of safety-net hospitals to provide patient-centered care by examining four questions: first, how well do SNHs provide patient-centered care compared to non-SNHs based on the metrics from the Hospital Consumer Assessment of Healthcare Providers and Systems (HCAHPS) survey? Second, over the four years during which patient experience has been publicly reported, have SNHs improved their performance to the same degree as other hospitals? Third, are there certain subgroups of hospitals where being a safety-net hospital is associated with particularly poor levels of performance? And finally, how do SNHs currently fare in relation to achievement thresholds used in the Value-Based Purchasing (VBP) program under the Affordable Care Act to pay or penalize hospitals through quality-based payment changes?

Our sample consisted of 3,096 hospitals surveyed in 2010. We found that safety-net hospitals had substantially lower performance than non-safety-net hospitals on nearly all measures of patient experience. The greatest differences in scores were observed in measures of the overall hospital rating, where 63.9% of patients in safety-net hospitals rated the hospital a 9 or 10 on a 10-point scale compared to 69.5% of patients in hospitals serving the lowest proportion of poor patients. Gaps were also sizeable for the proportion of patients receiving discharge information (2.6% difference, p<0.001) and for always communicating well with physicians (2.2%, p<0.001). The gaps in performance between SNHs and hospitals that serve the lowest proportion of poor patients were sizeable, and persistent over time, with little evidence that the gap was narrowing. The performance disparity was largest in hospitals located in the Northeast, and smallest in hospitals in the South. SNHs were much less likely to have scores at or above the median on all eight HCAHPS measures used in pay-for-performance policies, and much more likely to have no scores at or above the median, suggesting that SNHs are likely to fare poorly under the VBP payment scheme.
Characterization of neural development in the Tubb3 knockout mouse

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The microtubule cytoskeleton is essential for many cellular functions in the mammalian nervous system, including the establishment of cellular morphology, neuronal migration, and the development and maintenance of axonal and dendritic processes. Microtubules are composed of heterodimers of the homologous proteins - and ®-tubulin, which polymerize into protofilaments then assemble laterally to form cylindrical microtubules. Multiple isotypes of - and ®-tubulin exist in humans, each of which is encoded by a different gene. Although different isotypes can have unique spatial and temporal patterns of expression, the reason for multiple isotypes remains unknown.

Certain missense mutations in TUBB3, the gene that encodes the neuron-specific ®-tubulin isotype 3 (TUBB3), cause congenital fibrosis of the extraocular muscles type 3 (CFEOM3), a rare ocular motility disorder that results from aberrant growth of ocular motor neurons. Individuals harboring TUBB3 mutations may have CFEOM3 in isolation or with other stereotyped neurologic findings suggestive of perturbed axon guidance. Other specific missense mutations in TUBB3 cause malformations of cortical development in the absence of CFEOM3.

Consistent correlations between the individuals’ mutations and their neurologic phenotypes suggest that each TUBB3 mutation selectively disrupts specific processes in neuronal development or maintenance. However, the relative contribution of TUBB3 protein loss to these individuals’ phenotypes is unclear. In addition, little is known about the normal role of TUBB3 in neurodevelopment. To address these questions, we generated a TUBB3 knockout mouse and are characterizing its phenotype using histologic, biochemical, cell culture, and behavioral methods. Defining the knockout mouse phenotype will allow us to explore the role of TUBB3 in development and to elucidate whether any of the human TUBB3 phenotypes result from protein loss rather than perturbations in specific TUBB3 functions.
Breast cancer is the most common malignancy found in women, and as the second-most common cause of cancer death, is responsible for an estimated 40,000 deaths annually in the United States. Estradiol, acting via the estrogen receptor (ER), is a key regulator of mammary gland development. Approximately 70% of human breast tumors express ER, and the ER signaling pathway has been extensively targeted in treatments utilizing estrogen synthesis inhibitors such as aromatase inhibitors and ER modulators such as tamoxifen and raloxifene. Although such treatments have proven effective, tumor relapse is not uncommon and endocrine resistance eventually ensues in metastatic disease. Furthermore, toxic side effects are commonplace with these therapies.

Using recently established techniques to separate developmental subsets of normal human mammary epithelial cells, we perform genome-wide analysis with chromatin immunoprecipitation and gene sequencing (ChIP-Seq) to identify and characterize the target genes and cooperating transcription factors of ER in sorted mammary epithelial cell subpopulations. This data will then be compared to the ER-expressing breast cancer cell line MCF-7 and other ER-positive tumor models. By characterizing similarities and differences between the ER cistrome of normal human breast tissue, mutation carrier breast tissue, and breast tumors, we hope to identify novel predictive biomarkers and potential specialized therapeutic targets specific to ER-positive breast tumors and better understand the relationship between normal and malignant mammary cells.
Signaling Pathways in Mechanotransduction of Bone Cell Networks

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Osteocytes, encapsulated in a fluid-filled mineralized matrix forming an extensive network in the lacunae-canaliculari system, are believed to be key mechanosensors in bone adaptation and bone homeostasis. However, little is known about the signaling mechanisms by which the osteocyte network processes physiological mechanical stimuli. Calcium signaling, which is involved in many cellular processes, is likely linked to the underlying characteristics of the osteocyte and its mechanoregulatory function.

The objective of this study was to investigate intracellular calcium \([\text{Ca}^{2+}]_I\) oscillations observed in osteocyte-like MLO-Y4 cell networks, and to examine mechanisms that mediate multiple calcium spikes in such networks. Using well-established micro-contact printing and self-assembled monolayer (SAM) technology, osteocyte-like MLO-Y4 cells were micro-patterned in a network with a precisely controlled topology that closely resembles that in vivo, preserving the formation of cellular processes and gap junctions. Pathway studies investigating the role of phospholipase C (PLC), adenosine triphosphate (ATP) and T-type voltage-sensitive calcium channels (VSCC) were performed to identify the molecular mechanisms responsible for the calcium oscillations of osteocytes under fluid flow stimulation. Inhibitors that specifically target each of these pathways were introduced during the application of fluid shear stress on osteocytes placed within a parallel-plate flow chamber.

Our findings confirmed the critical role of phospholipase C, adenosine triphosphate, and T-type voltage-sensitive calcium channels in the modulation of calcium mobility into and within osteocyte cell bodies. Results showed that osteocyte-like MLO-Y4 cells share similar characteristics with osteoblasts in the context of PLC-and IP₃-mediated calcium release in response to shear stress. The T-type VSCC, which have established pacemaking and repetitive firing activity in cardiac and neuronal cells, may contribute to the characteristic oscillatory \([\text{Ca}^{2+}]_I\) response in osteocytes due to mechanical stimuli. Additionally, the differing expression pattern of T-type VSCC between osteocytes and osteoblasts may contribute as to why osteocytes are more responsive in calcium signaling than osteoblasts under fluid flow stimulation.

Ongoing work entails siRNA-mediated knockdown of T-type VSCC in osteocytes and expression of T-type VSCC in osteoblasts. Taken together, our work contributes to elucidating the mechanisms that contribute to calcium oscillations in osteocytes and to qualify them as the orchestrator of the bone modeling and remodeling process.
Effect of Rosiglitazone on Human Mesenchymal Stromal Cell Differentiation into Osteoblasts or Adipocytes

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Many studies indicated that age-related factors affect skeletal growth, but these mechanisms are not well understood in adolescents. Obesity, which increases risk of diabetes mellitus (T2DM), is an increasing concern in adolescents. Rosiglitazone, a treatment for T2DM, has been associated with increased fracture risk in patients through different mechanisms in adults and adolescents: adults have increased bone resorption via osteoclast activity, while the younger animals have decreased bone formation rate without a change in osteoblasts or osteoclasts. Thus, differentiation of MSCs provides an experimental tool for understanding the effect of adiposity via rosiglitazone in bone formation by comparing its effects on osteoblasts and adipocytes in vitro.

Our purpose was to assess the effect of rosiglitazone on differentiation of MSCs (age, gender, and BMI) through osteoblasts (runx2) or adipocytes (PPARgamma). We hypothesized increased adipogenic and decreased osteogenic differentiation via PPARgamma activation.

hMSCs (n=2) were isolated from iliac crest bone graft. Low-density human marrow mononuclear cells were isolated (Ficoll/Histopaque 1077). Two specimens were analyzed (10M with BMI=17.2, and 10F with BMI=23.2). When cells were confluent, they were placed in adipoblastogenic and/or osteoblastogenic medium and treated with rosiglitazone (1 μM and 10 μM), vehicle (DMSO), and no treatment for 5 days. RNA was isolated (Trizol), and RNA (2 µg) was reverse transcribed into cDNA, which was used for PCR reaction (primers runx2, PPARgamma). Concentrations of cDNA and amplification conditions were optimized for each gene product to reflect the exponential phase of amplification. PCR products were separated with 2% agarose gel electrophoresis and quantified by densitometry. Gene expressions were normalized to glyceraldehydes-3-phosphate dehydrogenase (GAPDH).

The high concentration of rosiglitazone decreased PPARgamma, and no expression of PPARgamma was present in osteogenic medium. However, the rosiglitazone had different expressions of PPARgamma: one subject had increased levels of PPARgamma versus no treatment (1.48; 1.05), while the other had decreased expressions of PPARgamma (0.55; 1.14).

Runx2 expressions were different in the two specimens. One specimen (10M, low BMI) showed no expression of runx2 with the treatment of rosiglitazone in the adipogenic media, and decreased expressions of runx2 in the osteogenic media versus no treatment (0.10; 0.27). The specimen from the other subject (10F, high BMI) expressed runx2 in all conditions: decreased levels of runx2 (1.06; 1.49) with rosiglitazone (1 μM) in adipogenic media and increased expression of runx2 in the osteogenic media (1.13; 0.79). These preliminary findings lead to the hypothesis that BMI and gender have influence on hMSC differentiation via rosiglitazone.
Epistaxis Management in a Tertiary Care Hospital

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Introduction: Epistaxis is a common medical emergency accounting for approximately 0.5% of ED visits in the US. Currently, there are several published papers providing guidance for treating epistaxis. However, none of these include rigorous data analysis and statistical comparison between interventions to support its conclusions.

Methods: We reviewed the electronic medical records of 177 patients who were treated for epistaxis at the Massachusetts Eye and Ear Infirmary between January 2005 and July 21, 2011. To be included in the study, patients had to have had an intervention for epistaxis at MEEI and be at least 18 years of age. The exclusion criteria were post-surgical epistaxis, hereditary hemorrhagic tangelectasia, and von Willebrands Disease. The medical records were reviewed and data, including past medical history, medications, and laboratory values (including coagulation studies and platelet count) were recorded. We also collected information about the patient’s experience at outside hospitals and at MEEI, including the number of bleeding episodes and the interventions used to control the epistaxis. Length of stay and complications were also recorded. Finally, we reviewed follow up notes when available to determine whether the intervention for epistaxis was successful.

Results: In patients for whom the site of bleeding was easily identified and accessible for cautery in the outpatient setting, this intervention was highly effective in resolving epistaxis. If nasal packing failed two times, the likelihood of success was quite low in our sample. If the same type of packing failed twice, in virtually no cases was that type of packing successful on the third attempt. In such a case, a more definitive approach, such as sphenopalanatine artery ligation was found to be effective. While few patients in our sample underwent embolization, this procedure was also effective in controlling the epistaxis.

We believe that our sample is generalizable. We had a fairly even distribution of men and women and a wide range of ages (18-90s). Some of the most common comorbidities were hypertension, dyslipidemia, and CAD. Additionally, many patients were taking aspirin, warfarin, and other anticoagulant therapies at the time of epistaxis.

Conclusions: Preliminary review of the data has revealed a few trends. It appears that otolaryngologists should avoid nasal packing in any one patient more than two times. If a site of bleeding can be identified and accessed for cautery, this procedure should be strongly considered. We found artery ligation and embolization to be safe and efficacious interventions for refractory epistaxis.
Prognostic factors associated with temporomandibular joint arthroscopy and arthrocentesis failure

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Purpose: The purpose of this study is to identify patients at the Massachusetts General Hospital who have had arthroscopic temporomandibular (TMJ) surgery or arthrocentesis for temporomandibular dysfunction (TMD) and fail to improve, and evaluate the prognostic factors associated with unsuccessful outcomes for each procedure.

Patients and Methods: This is a retrospective cohort study. The study population included all patients at the Massachusetts General Hospital (MGH) who have had TMJ arthroscopy or arthrocentesis from October 2004 to June 2011 were identified through the MGH Department of Oral and Maxillofacial Surgery data registry. We evaluated past medical and past dental history, including past TMJ treatment; presenting factors including pain level, presence of noise, and maximum interincisal opening (MIO); MRI findings including meniscal position and presence of degenerative changes, effusion, and remodeling; finding of arthroscopy including presence of adhesions, fibrillations, inflammation, and hyperemia; and postoperative factors including treatment regimen and follow-up MIO, pain level and complaints. Outcome was assessed based on improvement of MIO and pain level. The two groups, arthroscopy and arthrocentesis will be evaluated individually.

Results and Conclusion: Results are pending as data collection and analysis are ongoing.
Peripheral pulmonary stenosis (PPS)—narrowing of the branch pulmonary arteries (PAs) without major associated heart disease—can cause elevated right ventricular (RV) pressure, RV hypertrophy, and cardiac failure. PPS is often associated with Williams syndrome or other elastin deficiencies. Angioplasty and stent implantation have been shown to increase vessel diameter and decrease RV pressure acutely in the context of PA stenosis associated with other conditions, and are accepted primary therapies for PPS. But little is known about the long-term effectiveness of transcatheter therapy in infants and young children with severe PPS.

We undertook a retrospective cohort study of patients ≤5 years of age who underwent primary transcatheter intervention for severe PPS at Children’s Hospital Boston between 1984 and 2009. 69 patients constituted the study cohort. The median age at first intervention was 16 months. Syndromic/genetic diagnoses included Williams syndrome in 23 patients, and non-Williams familial arteriopathy in 12 patients. At the first intervention, median RV:aortic pressure ratio decreased acutely from 1.00 to 0.88 (pairwise median decrease of 0.18, p<0.001). Higher pre-intervention RV:aortic pressure ratio was associated with greater decrease in RV:aortic pressure ratio (p<0.001).

At a median cross-sectional follow-up of 8.5 years, 10 patients (14%) had died: 5 due to complications from PA catheterization (all before 1998), 2 following other cardiac procedures, and 3 in the community. Freedom from transcatheter reintervention was 47±7% at 1 year and 24±6% at 5 years. 13 patients underwent surgical PA augmentation, 8 within 1 year, and 11 together with repair of other major cardiac anomalies. Among the 41 patients who had a catheterization at least 1 year following the initial catheterization, the median RV:aortic pressure ratio had decreased from 1.0 at the first catheterization to 0.53 at the most recent (median decrease of 0.47, p<0.001). 40 (82%) out of 49 patients with clinical follow-up status available (median 8.5 years) had no cardiac symptoms.

While the absence of a control group precludes definitive conclusions about the relative benefit of transcatheter therapy for severe PPS, our data show strong long-term outcomes. The median patient is surviving, free from surgical reintervention, and asymptomatic, with approximately half systemic RV pressure. Long-term mortality secondary to RV hypertrophy was not observed despite the severity of initial disease. Procedural mortality was a significant hazard and was concentrated early in the study period, prior to the adoption a new technique, the creation of an atrial septal defect prior to PA dilation.
The Effects of Academic Partnership on Surgical Output at a Rural Rwandan District Hospital

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Background: The global disparities in access to health care between high- and low-income regions are immense and increasingly well documented. The vast majority of international health efforts have focused on reducing disparities in communicable diseases, namely HIV/AIDS and tuberculosis. Conversely, little has been done to address the lack of access to surgical care in resource poor regions. Since surgically treatable conditions are a main contributor to morbidity and mortality globally, it is necessary to develop mechanisms for improving access to surgery, particularly in rural areas. The Center for Surgery and Public Health at Brigham and Women’s Hospital has partnered with the Rwandan Ministry of Health and Partners in Health – Rwanda to carry out an academic intervention at three district hospitals in rural Rwanda. This study will assess the efficacy of this intervention in improving surgical output by comparing measures of surgical volume and mix pre- and post-intervention.

Methods: Surgery ward and theatre logs from Butaro Hospital, a 150 bed district hospital in Rwanda, were translated and entered into an electronic database for the purpose of quality improvement in accordance with Institutional Review Board and Ministry of Health (MOH) approvals. The World Health Organization International Classification of Disease (WHO/ICD-10) coding scheme was examined for its organizational structure. Existing Rwandan MOH morbidity reporting requirements were reviewed. Based on this information and considering the context-specific limitations on diagnostic accuracy and specificity, an adapted coding scheme was constructed and applied to the data. Overall surgical volume and case mix was then determined for the same three-month intervals in 2008, 2009 and 2010 to control for seasonal changes in hospital admission and surgical need.

Results: The total number of surgical cases performed at Butaro Hospital increased by 32% between 2008 and 2009, and by 31% between 2009 and 2010. Changes in case mix were found to correlate specifically with the presence of specialists. For instance, the presence of an obstetric surgeon in 2009 coincided with an increase in complex obstetric and gynecologic surgeries such as hysterectomies.

Conclusion: The presence of academic partnership at Butaro Hospital in Rwanda seemed to improve overall surgical output in terms of volume and case mix. However, this data should be further analyzed and compared to information from other rural hospitals to better understand the efficacy of this intervention.
Cerebral Palsy (CP), a nonprogressive perinatal brain lesion that leads to deficits in motor control, coordination, and function, is the most common cause of physical disability affecting children in developed countries with an incidence of 2 per 1000 live births. Hip dysplasia in CP has an overall incidence of 30% from large population based studies.

Proximal varus osteotomy of the femur (VDRO) is a well-established procedure in the management of hip dysplasia associated with CP. The rate of revision surgery after femoral osteotomy is variable within the literature from 10-60%. The purpose of this study is to report the medium term success of VDRO in children with CP and identify factors predictive of revision VDRO.

Gross motor functional classification system (GMFCS) is the universal language to describe motor dysfunction in children with CP, where a higher GMFCS indicates greater physical disability. A higher GMFCS and younger age at initial femoral osteotomy were hypothesized to be associated with increased rates of revision surgery in this study.

We performed an IRB-approved, retrospective review of all children with CP who underwent VDRO for hip displacement between January 1994 and December 2007. Age, gender, GMFCS level, previous hip surgery or Botulinum toxin administration, adjunctive pelvic osteotomy and presence of bilateral surgery at index procedure were analyzed by multivariable analysis to determine factors associated with need for revision. Surgical failure was defined as additional bony or soft tissue surgery performed after VDRO.

In total 648 VDROs in 370 children at a median follow-up of 6.7 years were recorded. The revision rate was 16% (106/635 hips). Survivorship after VDRO was 98% (635 hips) at 1 year, 92% (598 hips) at 3 years and 89% (579 hips) at 5 years. Logistic regression confirmed that age at surgery (p<0.0001) and GMFCS (p=0.004) were significant independent predictors of revision VDRO. Patients who underwent VDRO under 8 years of age and those with GMFCS level over 3 experienced higher rates of revision VDRO.

Management of hip displacement in children with CP is challenging. Our analysis reveals a moderate revision rate after VDRO of 11% at 5 years and 16% overall. These results illustrate the paradox of hip surgery in children with cerebral palsy – children who are most affected (young age of presentation) and need the surgery the most (high GMFCS level) have the highest revision rates.
Analysis of Food Assistance Packages for People Living with HIV Provided by PEPFAR/Viet Nam Partners

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Food and nutrition activities are important components of all care and treatment programs for the management of HIV and AIDS at all stages, from prevention to long-term care. Food and nutrition interventions can keep people living with HIV (PLHIV) healthy longer and improve their response to treatment.

The Food and Nutrition Technical Assistance Project II (FANTA-2) supports a nutrition assessment, counseling, and support (NACS) approach to prevent and treat malnutrition for PLHIV and encourage adherence to anti-retroviral therapy (ART). However, in Viet Nam there are currently no guidelines or recommendations on how to provide food assistance to PLHIV, nor is there any ready-to-use therapeutic food (RUTF) for the treatment of severe acute malnutrition (SAM) or moderate acute malnutrition (MAM). Beginning in 2007, the U.S. President’s Emergency Fund for AIDS Relief (PEPFAR)/Viet Nam began to authorize use of PEPFAR funds for food assistance to PLHIV. Various PEPFAR/Viet Nam partners implemented nutrition and food assistance programs which provided different commodities and had different program objectives and entry/exit criteria, locations, and duration of client support. In 2011 PEPFAR/Viet Nam announced that it was no longer supporting food assistance for PLHIV and requested that organizations begin to phase over and integrate their assistance with the Government of Viet Nam (GOV).

In this context, in June and July 2011 FANTA-2 conducted an assessment of the nutrition and food assistance programs currently implemented in Viet Nam to come up with recommendations for phase-over and integration of food assistance programs with existing GOV activities. The assessment also aimed to suggest a systematic and standardized process for planning food assistance, including how to choose food rations taking into consideration economic value, transfer value, nutritional value, transportability, and acceptability of food.

This report is a compilation of findings on current nutrition and food assistance programs in Viet Nam, implemented by both non-governmental organizations (NGOs) and the GOV. Recommendations for phase-over and integration strategies for food assistance programs are also included.
Prognostic Factors in Patients Undergoing Radiosurgery for Melanoma Brain Metastases

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The melanoma-specific Graded Prognostic Assessment (Melanoma-GPA) is a prognostic index for overall survival (OS) in patients with melanoma brain metastases. The Melanoma-GPA assigns patients a score between 0 (median survival time [MST]=3.4 months) and 4 (MST=13.2 months) based on two factors: Karnofsky Performance Status (KPS) and number of brain metastases. The purpose of this study is to validate the Melanoma-GPA and to identify other factors associated with OS, as well as factors associated with distant intracranial progression (DIP).

This was an IRB-approved retrospective analysis of patients treated with stereotactic radiosurgery (SRS) for melanoma brain metastases between 1/2000 and 6/2010 at two treatment centers in Boston. Patients were excluded if SRS was performed as salvage therapy or if it was performed only on a surgical resection cavity. OS and DIP were calculated in the remaining 147 patients using the Kaplan-Meier method. Prognostic factors were analyzed using the Cox proportional hazards model.

Median follow-up time for survivors was 23 months. Whole-brain radiation therapy (WBRT) was performed in 27% of patients and was associated with treatment center (p<0.0001) and >1 brain metastasis (p<0.0001). DIP occurred in 85 patients (58%), and median time to DIP was 2.8 months. On multivariate analysis, >1 brain metastasis (HR 1.9, p=0.009) and omission of WBRT (HR 2.1, p=0.006) were associated with DIP.

With a median OS of 7.3 months, there were 135 deaths (92%). Melanoma-GPA was associated with worse OS (score 0-1: HR 2.4, p=0.001), and MSTs were consistent with those predicted by the Melanoma-GPA. On multivariate analysis, KPS <90 (HR 1.5, p=0.03) and >2 ECD sites (HR 1.8, p=0.002) were associated with worse OS. Prognostic factors were also analyzed in the subset of 35 patients with absent or stable ECD. The only significant prognosticator for worse OS in this subset was >1 brain metastasis (HR 3.8, p=0.0004); with a HR of 1.9 (p=0.13), omission of WBRT did not reach statistical significance.

Our data provide validation of the Melanoma-GPA and suggest that ECD burden is an additional important prognostic factor for OS in patients with melanoma brain metastases. ECD status modifies the effect of intracranial disease burden on OS, such that >1 brain metastasis is prognostic for worse OS in patients with absent/stable ECD, but not in patients with progressive ECD. As new and better systemic treatments improve the ability to control ECD, the effect on OS of intracranial disease burden and control may become more significant.
Assessment of Health Indicators in Bwiza Village, Rwanda, to Provide Orientation to COPHAD Project

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Seattle-based Pygmy Survival Alliance (PSA) and their Rwandan partner Health Development Initiative (HDI) Rwanda have been active in a community of historically marginalized people in Bwiza, Ndera Sector, Gasabo District, near the capital city of Kigali, for approximately three years. In collaboration with other key partners, these two organizations have implemented a multidimensional project known as Community of Potters Health and Development Project (COPHAD) to combat malnutrition and reduce maternal and child mortality. During that time, there have also been numerous initiatives carried out by the Government of Rwanda to improve the health of all Rwandans.

The organizations conducted an assessment to determine what changes had taken place since a baseline survey of 27 households in early 2009 and to assess if there were any gaps in health indicators between the population of Bwiza and the national population. The intent was to identify programmatic priorities and to be better able to advocate for the community’s needs.

The survey tool used to assess health indicators among the population of Bwiza was based on Rwanda’s 2005 Demographic and Health Survey, and was an updated version of the one developed for the 2009 baseline survey. Survey topics include household demographics, available resources, and maternal and child health (prenatal care, nutrition, health care use, etc.). Interviews were carried out by a two-person team consisting of an American student and a Rwandan bilingual Kinyarwanda/English speaker. Thirty-four households (out of an estimated 58) were surveyed. When possible, the mother of each household provided responses to the survey; in households without mothers (e.g. single men or childless couples) an alternate individual was selected.

Data is still being analyzed; however, preliminary results show several significant changes, including more households with access to pit latrines, greater use of antenatal visits, increased recent protein intake, and a greater proportion of people holding valid insurance cards.
Palliative Care Rapid Situation Analysis in Neno, Malawi: Summary of Stakeholder and Service Provider Interviews

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Background: Access to comprehensive palliative care (PC) services for patients with chronic, serious illnesses remains limited in sub-Saharan Africa despite recent progress in some countries. In Malawi, formal inpatient PC services have been provided largely at central level and at a few district hospitals. Even with MOH-supported PC training, national PC guidelines, and plans for scale up of PC services in place, PC service coverage remains patchy or non-existent, especially in rural settings like Neno District. To determine the scope of available services and to set priorities for future implementation, the first part of a rapid situation analysis of PC services in Neno District was completed in summer 2011. Part two will be carried out in January 2012.

Methods: Key stakeholder and provider interviews at both central and district levels, and a review of relevant documents, forms, and reports, were completed as of August 2011. Interviews with patients and their family members or caregivers will be initiated after IRB approvals are obtained in Malawi and Boston. Standardized, translated instruments adapted from prior PC situation analyses were and will be employed for all interviews.

Preliminary Results: Healthcare providers had positive attitudes about the importance of PC in general, good knowledge regarding the scope of PC, and seemed comfortable providing opioids when indicated. Despite difficulties with medication procurement at the central level, most essential medications were currently in stock in the district hospital and one community hospital in Neno and had been in stock for the previous six months. Though providers had received general exposure to PC in their pre-clinical or clinical curricula, few had received the MOH-sponsored training or had exposure to the new PC guidelines. Constraints in provider time, physical space, and transportation were commonly sited as barriers to providing PC.

Preliminary Conclusions: There has been significant recent progress in PC in Neno District. Despite human resource constraints, next steps could include increased training and supervision, implementation of PC at the community level, and carefully designed task shifting. Completion of additional interviews and analyses will be useful not only to inform quality improvement efforts in Neno, but also to provide an example of a rapid assessment that can be replicated and to contribute to the existing literature on palliative care in resource-limited settings.
Religious/Spiritual Care Provided by Oncology Physicians and Nurses to Advanced Cancer Patients

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For many patients facing a diagnosis of advanced cancer, religion and/or spirituality (R/S) often play an important role in coping with illness. Research has shown that many such patients report their R/S to be integral to the course of their cancer experience and that patients frequently desire attention to their R/S as a component of their end-of-life care. Finally, data also suggest that cancer patients receiving spiritual care are more satisfied with their care; have better quality of life at the end of life; and receive less futile, aggressive interventions at the end of life. As a result of these findings, national palliative care guidelines include spiritual care – attention to patient R/S as part of medical care – to be a key component of end-of-life care. However, the exact role that clinicians should play with respect to provision of spiritual care is unclear. In this study, we sought to characterize current spiritual care practices by oncology physicians and nurses, as given to terminal cancer patients. Furthermore, we sought to understand the factors that predict whether or not a physician or nurse will provide spiritual care to their patients.

The data for this project are from the Religion and Spirituality in Cancer Care (RSCC) study, a survey-based, cross-sectional study of oncology practitioners (physicians and nurses) and advanced cancer patients from five Boston-area academic institutions. The survey gathered information including respondents’ R/S beliefs and practices, their views on the appropriateness of spiritual care in the advanced cancer care setting, and their experiences in giving or receiving spiritual care. In total, we received responses from 68 patients [response rate (RR)=73%], 204 physicians, and 114 nurses (RR=64%).

We found that oncology physicians and nurses reported providing spiritual care infrequently. When asked about their last three advanced cancer patients, 83% of doctors and 86% of nurses reported not taking a spiritual history for any of these three patients. Additionally, only 26% of doctors and 35% of nurses reported providing any chaplaincy referrals to those same patients. We also examined predictors of spiritual care provision. Prior training in spiritual care was significantly associated with spiritual care provision (OR for physicians 5.89, CI 2.14-16.22; OR for nurses 10.42, CI 1.30-89.19). Providers identifying themselves as being spiritual were also more likely to provide spiritual care (OR 3.85 for physicians CI, 2.12-6.98; OR 2.92 for nurses CI, 1.15-7.42).

These data highlight the current inadequacies of spiritual care provision by physicians and nurses, despite national palliative care guidelines. Furthermore, these findings underscore the central role of spiritual care training for doctors and nurses, as this was the strongest predictor of spiritual care provision. Given the important role that spiritual care has in end-of-life care and the paucity of data guiding its provision, we hope that this research will advance the understanding of how to integrate spiritual care into end-of-life care, and ultimately improve patient outcomes at the end-of-life.
Timing of Lingual Nerve Repair

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The purpose of this study was to investigate the relationship between timing of lingual nerve repair and functional sensorial recovery.

The authors used a retrospective cohort design to assemble a cohort of subjects who underwent lingual nerve repair. The primary predictor variable was repair status, classified as early ($\leq 90$ days between injury and repair) or late ($\geq 90$ days between injury and repair). The outcome variable was the achievement of functional sensorial recovery (FSR) determined by standardized neurosensory examination. Cox proportional hazard modeling was used to evaluate the association between the variables collected and FSR.

The cohort consisted of 55 subjects, undergoing lingual nerve repair between October 2004 and December 2010. Twenty-four (43.6%) patients achieved FSR and the majority of those patients, 16 (29.1% overall), achieved FSR within one year. Nine subjects (16.4%) underwent early repair, 6 (66.6%) of which achieved FSR compared to only 18 of the 46 (39.1%) patients undergoing late repair ($P=1.13$).

While this study only found evidence suggesting a correlation between repair status and FSR. It is now clear in the field that early repair offers clinical benefit to patients. Notably, despite recommendations in recent years this study found no increase in the percentage of patients undergoing early lingual nerve repair as compared to the previous studies which first showed a correlation between early repair and FSR.
Baseline Qualitative Study For Oral Health Development Programs In Mayan Villages Of Toledo, Belize

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Thirty-nine dentists provide care to 320,000 residents of Belize. The poorest district with the largest Mayan population, Toledo District, has one dentist providing care to 30,000 people, although two dental operatories exist. A needs assessment performed in Oct 2010 found an absence of supplies and providers, no plan for provision of providers, a reliance on missionary groups for care, and dentistry as the most often cited health need in the community.

A seven week pilot study was conducted to gather preliminary qualitative data primarily on economics, and also on beliefs, hygiene, infrastructure and transportation for Child Dental Relief, Inc.’s oral health development programs for the community. Observations and semi-structured interviews were conducted at ten Mayan Villages throughout Toledo District. Disposable income, health costs, household financial management, cultural aspects and seasonal effects on finances were assessed. Interviews were conducted with the local dentist, hospital administrators, the Senior Dental Surgeon of Belize, and local missionary groups to assess provider incentives.

The population is taught oral hygiene through the public school system, and maintaining oral health does not contradict any cultural beliefs nor is inhibited by a lack of supplies or water. A lack of knowledge of proper oral care for children exists, as many do not begin to brush their teeth until they learn in public school. Public transportation, via bus, to the dentist is reliable but expensive and can take up to two and a half hours one-way. Social Security only covers the cost of extractions for the general population and cleanings for diabetic, prenatal and hypertensive patients. Interviewees and providers voiced a need for coverage for preventative and restorative care, which is provided sporadically by various missionary trips to the villages. Belize is short of providers because there is no dental school and few people can afford international schooling.

On July 17, 2011 the Belizean Ministry of Health addressed dental health issues and commemorated the donation of nine mobile dental units for use in rural communities. In collaboration with the government, sustainable care can be established through the provision of a scholarship for a local student to attend dental school, on contract to staff the empty dental operatory. Local health care providers should instruct mothers how to maintain oral hygiene for their young children. The establishment of an externship program for dental students through Hillside Clinic should be considered.
Investigating Programmatic Approaches for Improving Nutrition in Indigenous Communities in the Rural Peruvian Andes

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Approximately 30-40% of children under age five are chronically malnourished in rural Peru. In indigenous communities in the rural, high-altitude Calca Province, rates of chronic malnutrition in children are even higher; for example, a 2001 survey in Calca communities found that 66.1% of children were chronically malnourished. Chronic malnutrition in children causes stunting, impaired cognitive development, and increased susceptibility to infectious diseases.

Many interventions to address chronic child malnutrition in resource-poor settings have been attempted worldwide with varying effectiveness. General approaches include micronutrient supplementation, the provision of supplementary food products or food subsidies, and education and behavior-change programs. Although some interventions have produced favorable results, the literature shows that poverty and community-specific context are essential in considering the viability of any given approach.

This service project provided programmatic support for a Peruvian NGO, DESEA Perú (DESEA), that wished to expand its nutrition program in Calca. The project involved two primary components: (1) to interview community members and nutrition stakeholders in Calca about which approaches to addressing child malnutrition are best, and (2) to review scholarly literature on nutrition programs targeting high-altitude, indigenous, and/or rural communities in Peru. Together with the community, DESEA intended to use project findings to create a community nutrition strategy.

Before the project commenced, DESEA emphasized that qualitative rather than quantitative information was most important in helping the organization and community move forward. Thus, interviews were informal and did not include a written survey instrument. Interview subjects were selected based on the participants’ community role or relevant expertise. Scholarly articles were selected based upon information elicited during the interviews.

The final deliverable to DESEA was a 26-page report that included an analysis of government nutrition programs, a section with abridged notes from interviews with 25 subjects, an extended annotated bibliography on nutrition in Peru, and a commentary with programmatic suggestions.

This project found that no single solution will adequately address chronic malnutrition in Calca, and that culturally and historically relevant programs must be developed. Although many stakeholders in Calca are not proponents of government social programs that address child malnutrition, much evidence shows that these programs are relatively effective. These programs can work better if they cater more appropriately to the population. Political and ideological discord between the local government, the Peruvian health system, and NGOs has hindered progress in improving child malnutrition.
The Association Between Physical Activity and the Risk of Incident Psoriasis

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Objective: To examine the association between total physical activity, walking, and vigorous exercise and the incidence of psoriasis in women.


Main Outcome Measure: Risk of psoriasis by quintile of physical activity as measured by metabolic equivalent task score.

Results: We documented 1026 incident psoriasis cases during 1,195,703 person-years of follow-up (14 years, 1991-2005). After adjusting for age, smoking, and alcohol use, increasing physical activity was inversely associated with the risk of psoriasis. The most physically active quintile of women had a lower multivariate relative risk (RR) of psoriasis (0.72; 95% confidence interval [CI], 0.59-0.89; P for trend <.001) when compared to the least active quintile. Vigorous physical activity (≥6 metabolic-equivalents) was associated with a reduced risk of psoriasis (multivariate RR for highest quintile, 0.66; 95% CI, 0.54-0.81; P for trend <.001); this association remained significant after adjusting for BMI (RR, 0.73; 95% CI, 0.60-0.90; P for trend .009). Walking was not associated with psoriasis risk. In a subset of 550 confirmed psoriasis cases, we observed a similarly reduced risk of psoriasis associated with vigorous physical activity (multivariate RR for highest quintile, 0.64; 95% CI, 0.48-0.86; P for trend .03).

Conclusions: In this study of US women, vigorous physical activity was independently associated with a reduced risk of incident psoriasis.
Connexin50 requires p150 to form Gap Junctions

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Background and Objectives: Connexins form the intercellular channels that comprise gap junctions. The ocular lens expresses three connexins, Cx50, Cx43 and Cx46, all of which are critical for adult lens homeostasis. All three have a PDZ-domain binding motif at their C-termini and been shown to bind the scaffolding protein ZO-1. However, Cx50 requires ZO-1 binding to form intercellular channels in HeLa cells while Cx43 does not, suggesting that these connexins utilize different assembly mechanisms.

Some aspects of the Cx43 assembly pathway have been defined. Cx43 is packaged into vesicles via the classical secretory protein pathway then trafficked directly to adherens junctions at areas of cell-cell apposition by a mechanism requiring microtubules and EB-1, a microtubule plus-end tracking protein. P150, a component of the dynein/dynactin complex localized to adherens junctions, plays a crucial role in this delivery process by binding EB-1, thus anchoring the microtubules and facilitating delivery of Cx43 into gap junctional plaques. To explore the generality of the model proposed for Cx43, we tested whether Cx50 also requires p150 for junction assembly.

Methods: A HeLa cell subclone selected for the lack of endogenous gap junctions was transfected with a mixture of siRNAs corresponding to p150 and incubated for 72 hours before a second round of transfection with plasmid encoding mouse Cx50. The intracellular distribution of Cx50 and p150 were assessed using indirect immunofluorescence with specific antibodies.

Results: Gap junctions stereotypically display as punctate regions of immunofluorescence at the surfaces of cells in regions where they come into contact. Parental HeLa cells display little immunofluorescence signal when stained with Cx50 antibodies (Fig.1) while those transfected with Cx50 display numerous small immunofluorescence puncta at appositional surfaces (Fig.2). Staining parental cells with antibodies against p150 reveals a diffuse but robust intracellular distribution and strong staining of what is likely the centriole, consistent with association of p150 with microtubules (Fig.3). Treatment of the parental cells with p150 siRNA for 72 hours dramatically reduces the diffuse intracellular fluorescence although the centriolar signal was only modestly affected. Cx50 expressed in p150 knock-down cells does not form obvious junctional plaques and is retained in what are likely intracellular membrane compartments (Fig. 4).

Conclusions: The results indicate that p150 is necessary for Cx50 to assemble into gap junctions. Together with previous studies, these data suggest that connexins share a common core assembly pathway in addition to connexin-specific ones.
Niacin-Induced Free Fatty Acid Suppression and Growth Hormone Concentrations in Obese Children

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Concurrent obesity increases the difficulty of assessing whether growth hormone (GH) deficiency exists in children with short stature. Obese children and adults display lower spontaneous and stimulated growth hormone (GH) secretion. It is presumed that dysregulation of some of the factors normally involved in controlling GH secretion underlies the hyposomatotropinemia of obesity, given that GH production usually normalizes after weight loss. Free fatty acids (FFA) are one factor thought to be involved in regulation of GH secretion.

Niacin is a nicotinic acid derivative that inhibits lipolysis and lowers circulating FFA concentrations. Specifically in obese adults, inhibition of lipolysis has been found to increase spontaneous and stimulated GH production, presumably due to direct effects of FFA on hypothalamic GH-regulating neurons. Thus far no pediatric studies have examined the effects of niacin on GH secretion, and there are no data in obese children demonstrating the effects of inhibition of lipolysis on GH secretion.

We conducted a pilot dose-determining study to study to examine how niacin affects FFA in obese children. Based on extrapolation from adult studies, we hypothesized that 250 or 500 mg of niacin, given every two hours by mouth for a total of three doses, would sufficiently suppress FFA concentrations to a level associated with an increase in stimulated GH concentrations. Five children, aged 7-12, were admitted to the NIH CRC for study. After an overnight fast, subjects were given three doses of Niacin (either 250 and 500mg/dose) per os q2h. FFA and GH were measured every 30 minutes for 360 minutes.

Children in the 500 mg Niacin treatment group had significantly lower FFA throughout the study than children in the 250 mg treatment group (p<0.05), with the largest difference observed at 360 minutes (1159±412 vs. 212±131 uEq/L, p=.03). Even when controlled for Body Surface Area, the 500 mg Niacin treatment group had significantly lower FFA than the 250 mg Niacin treatment group (p<0.05). Growth hormone concentrations showed nonsignificant trends towards higher concentrations in the 500 mg Niacin treatment group.

These pilot data indicate that a regimen of three doses of Niacin 500 mg per os q2h suppresses FFA to a significantly greater extent than a 250 mg dose schedule. FFA suppression resulting from the 500 mg regimen will next be tested to determine if it is sufficient to augment GH secretion during provocative GH stimulation tests in obese and non-obese children.
Implementation of Value-Based Insurance Design for Commercial Insurers

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Value-based insurance design (VBID) emerged from the observation that short-term savings in medical billing through increased patient cost sharing may lead to increases in long-term aggregate health care spending through the lowered use of necessary, high-value medical services. As such, VBID aims to incentivize patients and providers to utilize high value services. For people living with a chronic disease, in which clinical guidelines call for long-term management to avoid future complications, VBID offers the opportunity to encourage adherence to drug and preventive regimens through targeted reductions in co-pay and co-insurance rates. Encouraging medical adherence through reduced patient out-of-pocket payments can yield increases in health care quality while reducing overall spending from decreased hospitalizations and other high-cost interventions.

Analyses and simulations have highlighted the promise of VBID in achieving cost savings, and implementations of VBID among self-insured employers and commercial insurers have produced positive outcomes. To assess the feasibility of designing VBID disease-specific software modules for the commercial insurance market, employers, health plans and brokers were surveyed by the TriZetto Group on their goals for health care cost reduction and their needs for better employee health. Based on these results, clinical guidelines and comparative effectiveness research reports were reviewed to identify high-value health care services for treatment of diabetes and asthma, and specific services were selected and adapted for integration into a software-ready VBID benefits product for commercial insurers. Specific co-pay and co-insurance reductions for chosen services were considered in the context of extant literature.

The work led to the synthesis of two VBID clinical modules, one for diabetes and one for asthma, that describe the specific services to be subsidized for patients and, more uniquely, contain the specific diagnostic and service codes necessary for insurers to integrate the modules into their software systems. They were subsequently packaged and sold to two commercial insurers: currently, 3.1 million patients accounting for $10 billion in paid claims have access to VBID solutions. Initial feedback has been positive—VBID has the potential to reduce health care costs while enhancing the quality of delivered care to patients.
Baseline Qualitative Study For Oral Health Development Programs In Mayan Villages Of Toledo, Belize

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Of the thirty-nine dentists that provide care to the 333,000 people of Belize, only one dentist administers care to the 30,000 residents of the Toledo District, the poorest district that hosts the largest Mayan population. In October 2010, Dr. Sam A. Merabi of the Harvard School of Dental Medicine performed a qualitative needs assessment of Mayan villages within Toledo. The needs assessment established a lack of dental supplies and providers, no plan for the provision of providers, a reliance on missionary groups for care, and dentistry as the most commonly cited health need.

A seven-week pilot study was conducted to gather preliminary qualitative data focused on transportation and its effects on access to dental care. The study also gathered data on community economics, beliefs and hygiene practices in the communities. Observations and semi-structured interviews were conducted at ten Mayan villages throughout Toledo District. Modes of transportation, service routes to villages, seasonal effects on road conditions, accessibility and reliability of transport, necessity of transport and bus fares were assessed (n = 76). Interviews were conducted with the local dentist, hospital administrators, and the Senior Dental Surgeon to assess provider incentives.

It was determined that the population is taught oral hygiene through the public school system, although a lack of knowledge still exists. Maintaining oral health does not contradict any cultural beliefs nor is inhibited by a lack of supplies or water. Reliable buses exist, however bus fares are expensive, and several villages are either far or inaccessible via bus routes. Social Security only covers the cost of extractions for the general population, as well as cleanings for diabetic, prenatal and hypertensive patients. Interviewees and providers voiced a need for coverage of preventative and restorative care, which is provided sporadically by various missionary groups.

On July 17, 2011 the Belizean Ministry of Health addressed dental health issues and commemorated the donation of nine mobile dental units for use in rural communities. In collaboration with the government, sustainable care can be established. Conceivable ideas include the creation of a scholarship for a local student to obtain a foreign dental education contingent on his or her return to staff the operatory at Isabella Palma Polyclinic, the implementation of oral hygiene workshops hosted by local health workers, the initiation of a fluoridation program for children. Also, the establishment of an externship program for dental students through Hillside Clinic should be considered.
An integrated approach to the genetic diagnosis of mitochondrial disorders

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Defects in mitochondria, the organelles that generate cellular energy, can cause devastating disorders of energy metabolism. Collectively, these disorders affect 1 in 5,000 live births and many more patients are diagnosed with adult-onset disease. These disorders vary widely in severity and clinical presentation. Most patients experience a progressive course of disease characterized by worsening fatigue, exercise intolerance, and the involvement of multiple organ systems. The diagnosis of mitochondrial disorders is presently based on a collection of clinical, histological, and biochemical data.

Most genetic mutations underlying mitochondrial disorders are unknown. Mutations in mitochondrial DNA (mtDNA) account for approximately 20% of pediatric disease. The remainder of cases is likely due to variants in nuclear DNA, specifically the complement of over 1,100 genes that encode proteins localized to the mitochondria (the “MitoExome”). Among these genes, 77 have previously been identified as disease-related. Deep gene sequencing may facilitate the identification of more disease loci, thereby improving the diagnosis and management of patients with mitochondrial disorders.

We recruited 98 participants from the mitochondrial disorders clinic at Massachusetts General Hospital for sequencing of their mtDNA and 1,500 nuclear genes. We used hybrid selection and Illumina sequencing on this 3.1Mb target region. We developed a computational method to identify previously-reported pathogenetic variants and prioritize novel candidate disease variants from the large number of sequence variants detected within each sample. Patients’ variants were also compared with publically-available sequence data from a cohort of healthy controls.

Preliminary results show that, on average, patients with mitochondrial disease have twice as many prioritized variants than controls. Approximately 30% of patients have at least one nuclear-encoded candidate disease gene. To firmly establish pathogenicity of novel candidate genes, we are currently performing complementation experiments in patient cellular models of disease.

We also studied the clinical, biochemical, and histologic data from several patients in greater detail, to establish correlations between their prioritized variants and particular clinical presentation. Data from these case studies were presented at a series of multidisciplinary conferences, during which researchers and clinicians collaborated on diagnoses and began developing approaches to using exome sequencing as a clinical tool. MitoExome sequencing has the potential to determine novel disease loci and improve clinical diagnosis. Because of the vast phenotypic and genotypic heterogeneity of mitochondrial disorders, sequencing data must be carefully integrated with clinical information in order to determine the contribution of candidate variants to each patient’s unique features of disease.
Moyamoya Disease: 
Age and stage of presentation in pediatric patients with sickle cell disease
Health Disparities Scholars in Medicine Fellowship

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Object: Both sickle cell and moyamoya disease constitute significant risk factors for strokes; and the management of individuals with both conditions (MMD-SCD) remains controversial. Surgical revascularization promises significantly superior and effective results as compared to the current therapeutic approach (ie. exchange transfusions); however, it is essential that these patients come under neurosurgical attention early. Early detection and treatment of moyamoya – before major stroke has occurred – is associated with improved long-term outcome. This study seeks to specifically investigate when MMD is typically diagnosed in children with SCD and whether this occurs at a later age and stage than in non-SCD patients.

Methods: We reviewed age, clinical, and radiographic records of all patients who underwent a standardized revascularization procedure – pial synangiosis – for moyamoya disease at Children’s Hospital-Boston between 2005-2010. We characterized and compared data at time of MMD presentation for all patients with concurrent sickle cell disease and those without.

Results: We evaluated 134 MMD non-SCD patients and 13 MMD-SCD patients with male:female ratios of 60:74 and 7:6 respectively. Average age of presentation in years old was 7.619 (range 4 months to 20 years old) for MMD non-SCD patients and 11.385 (range 3-21) for the MMD-SCD population. Nine patients (69%) in the MMD-SCD pool suffered from bilateral disease as compared to 110 patients (82%) in the MMD non-SCD cohort. However, average Suzuki scores were higher in MMD-SCD populations-- 3.25 and 4.28 as compared to 3.24 and 3.13 in MMD non-SCD patients (Suzuki scores reported for left and right hemispheres respectively). We also calculated presence of infarcts per affected hemisphere to be 86% for MMD-SCD and 57% for MMD non-SCD patients. Furthermore, assessment of clinical records yielded a Modified Rankin Score of 2.00 for MMD-SCD and 1.76 for the MMD non-SCD patient pool.

Conclusion: Our study demonstrated that MMD-SCD patients come under neurosurgical attention at a later age and stage of moyamoya disease than do MMD non-SCD patients. A reason for this may be mischaracterization of early MMD as sickle cell symptoms, and could be best remedied by encouraging improved communication between hematologists and neurosurgeons. We propose that better collaborative measures be implemented to improve care for MMD-SCD patients and get them the proper therapy sooner.
The Role of Macrophages in PGC-1α Induced Angiogenesis in Skeletal Muscle

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Angiogenesis occurs in response many stimuli including ischemia, hypoxia, and exercise. The best known mechanism for induction of angiogenesis is the hypoxia inducible factor (HIF) mediated hypoxia response pathway. Arany et al (2008) recently discovered that PGC-1α, a transcriptional coactivator and important regulator of mitochondrial biogenesis, regulates a novel HIF-independent angiogenic pathway.

Studies in our lab show that constitutive overexpression of PGC-1α in skeletal muscle of transgenic mice triggers angiogenesis and results in an increase in the number of functional capillaries in the muscle. Additional studies of mice with a tetracycline-inducible, skeletal-muscle-specific PGC-1α transgene show that induction of PGC-1α expression for three weeks in adult animals also causes an increase in capillary and arteriole density.

We seek to characterize the cellular players and chemical mediators responsible for PGC-1α regulated angiogenesis. We conducted a microarray analysis of skeletal muscle from PGC-1α mice induced to express the transgene for four weeks. Data demonstrate increased expression of the chemokine osteopontin (SPP1) and macrophage activation markers including CD169 in transgenics as compared to wildtype. Immuno-histochemical staining for macrophage markers F4/80 and CD11b confirms an increased number of macrophages in the transgenics compared to wildtype.

To characterize the macrophage population we used flow cytometric analysis of interstitial cells from hindlimb skeletal muscle of wildtype and transgenic mice. We found that there is an M1-phenotype-skewed ("proinflammatory") population of macrophages in the muscle of transgenic animals. Although there was no increase in macrophage number via staining for CD11b and F4/80, analysis of cell size and scatter did show a significant increase in the macrophage/monocyte population.

Studies have shown that osteopontin may play a role in macrophage migration and angiogenesis. To determine if osteopontin plays a role in monocyte/macrophage activity in PGC-1α regulated angiogenesis we generated SPP1 knockout/PGC-1α transgenics. Immuno-histochemical staining of skeletal muscle and FACS analysis of muscle interstitial cells from SPP1 knockout/PGC-1α transgenics did not show a change capillary density or in macrophage number compared to PGC-1α transgenics.

To assess the direct effect of osteopontin on macrophage gene expression THP1 monocytes were differentiated into macrophages by treatment with PMA and incubated with conditioned media from osteopontin overexpressing 293T cells. qPCR analysis of these cells shows significant increases in expression of macrophage markers CD163, CD206, CD169 and the monocyte chemoattractant MCP-1. Therefore osteopontin may be partially responsible for macrophage activation in PGC-1α regulated angiogenesis although in vivo other redundant mechanisms are able to compensate for its absence.
Modeling CD4 T-cell recovery in AIDS patients with successful HAART: A genome wide association study with longitudinal data

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The rate of CD4 T-cell recovery has large variability among HIV/AIDS patients. While treatment adherence is the dominant determinant of successful HAART, genetic factors may help to explain the variability among individuals who achieve adequate viral load suppression. In this study we developed a model for incorporating longitudinal CD4 T cell data and performed a genome-wide study of CD4 recovery rate.

A total of 1801 individuals (868 of European descent, 523 of African descent, and 410 of Hispanic descent) were selected from 3395 individuals from 4 drug treatment trials from the AIDS Clinical Trials Group (ACTG) using the following criteria: (1) the patient viral load dropped below 200 copies/μl during first 48 weeks after initiating HAART and (2) the patient viral load was not above 200 copies/μl more than once within any 48 week period. DNA samples of these individuals were genotyped using the Illumina HumanHap 650Y and Human1M platforms. Single nucleotide polymorphisms (SNPs) with a genotype rate less than 95% and a minor allele frequency less than 1% were excluded from the analysis, leaving 523410 SNPs for the analysis. We modeled the CD4 data for the first three years of treatment using a linear mixed effects model, which included the minor allele count (SNP), SNP-time interaction, time, intercept, sex, and population structure covariates as fixed effects, and intercept and time as per-individual random effects. We calculated P-values for the SNP-time interaction and set genome-wide significance at $p<5.0\times10^{-8}$.

A SNP in the coding region of the $CREBBP$ gene was found to have genome wide significance in the Hispanic subgroup ($p=1.4\times10^{-8}$). This finding did not replicate in the European or African subgroups. Furthermore, the minor allele frequency of this SNP was relatively low (0.03) which increases the likelihood that the finding is a false-positive. We performed a meta-analysis of all 1801 individuals by combining p-values from the three subgroups using Fisher’s rule. No other genome-wide significant associations were found in the individual European or African subgroups or in the meta-analysis.

We estimated that this study had 72% power to detect a SNP effect explaining at least 2.0% of the variability in CD4 T-cell recovery. Further collaboration with other study populations would increase the power to detect SNPs of smaller effect size. Imputation of additional SNPs using 1000 Genomes Project data followed by gene-based and pathway-based testing methods may also lead to better understanding of the biological mechanisms governing CD4 T-cell recovery rate.
Pig Gastric Mucin Glycosylation Repels \textit{S. pneumoniae} Adhesion to Polystyrene

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\textit{Streptococcus pneumoniae} is the leading cause of bacterial pneumonia, meningitis, and sepsis in children worldwide, and challenges vaccine development due to the presence of over 92 serotypes, each with a distinct polysaccharide capsule and widely varying epidemiological parameters. Information on mucus adherence of \textit{S. pneumoniae} serotypes may help inform vaccine design as well as elucidate mechanisms of host innate defense. For this project, the adherence of eight serotypes on an identical genetic background to reconstituted pig gastric mucus (PGM) was measured using a quantitative mucus adherence assay developed in the Ribbeck laboratory. The aims were to correlate mucus adherence of \textit{S. pneumoniae} serotypes with the structural properties of the polysaccharide capsule as well as the biochemical properties of mucus.

Eight serotypes, ranging from small to large capsule size, were assayed. PGM monolayers (as well as multilayers) decreased adherence of all serotypes. Furthermore, large inter-serotype variation in mucin binding was observed and could be reproduced in 4 independent experiments. As the serotypes were cloned on a common genetic background, it is highly likely that the variation in mucus adherence between serotypes was due to variations in capsular structure. The mechanism of how variation in capsular structure led to varying degrees of mucus adherence was unclear; when the serotypes were arranged by capsule size, there was no noticeable trend in mucus adherence.

Based on the high sialic acid content of mucin as well as the previous finding that the polysaccharide capsules of the 92 serotypes are either neutral or negatively charged, we hypothesized that bacterial repulsion occurs via ionic interactions. To test this, we varied the ionic strength of bacterial media during plating to determine if charge screening would affect the mucus-bacterial interaction. Interestingly, bacterial binding was not significantly affected. Similarly, no trend was recorded after treating mucin with neuraminidase to remove negatively charged sialic acid residues. In contrast, after treating PGM with trifluoromethanesulfonic acid (TFMS) to extensively remove its polysaccharide branches and expose the hydrophobic core, binding increased.

Although \textit{S. pneumoniae} serotypes are repelled by PGM, this repulsion does not appear to be mediated by ionic interactions. Furthermore, although significant inter-serotype variation in mucus binding is observed, this variation does not appear to correlate to capsule size. Further studies into the mechanisms behind these observations will help inform vaccine design as well as identify aspects of innate defense which may be compromised in vulnerable patient populations.
Implementation of a community health worker training program addressing diabetes and hypertension in rural Guatemala

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Like many other low-income countries, Guatemala is experiencing an epidemiological shift to what has been characterized as the “double burden of disease.” Susceptible to infectious diseases and under-nutrition, many Guatemalans are developing chronic non-communicable diseases (CNCDs) such as diabetes mellitus and hypertension. The emergence of CNCDs imposes a significant burden on individuals and strained health care delivery systems and demands innovative forms of disease monitoring and intervention.

The community health worker (CHW) model of health care delivery has been implemented in communities around the world for over 50 years. Designed to fill gaps in health care delivery, CHW programs employ community members to render basic health services in their home communities. Community health workers represent a model of health care delivery particularly well suited to chronic diseases because they can bring medications directly to patients’ homes and thereby overcome logistical barriers to health care access. In the realm of CNCDs, there is growing evidence supporting the effectiveness of CHWs in controlling diseases such as diabetes and hypertension.

We developed a CNCD curriculum for a team of CHWs in the Huehuetenango region of Guatemala, and assisted with active case finding in CHW home communities. The regional director of Partners in Health provided clinical expertise and institutional support for medical supplies. Our sixteen-day course focused on diabetes and hypertension diagnosis and management. Teaching modalities included case presentations, didactic lessons, brainstorm sessions, and interactive games. The curriculum emphasized explanatory models for chronic diseases, lifestyle interventions, and titration and scheduling of medications for diabetes and hypertension.

We evaluated a total of 333 patients at five community outreach events, which were locally publicized and included free blood pressure and blood glucose checks and a medical consultation. Using standard diagnostic criteria, 19 patients (5.7%) were diagnosed with pre-hypertension, 52 (15.6%) with hypertension, 9 (2.7%) at-risk for diabetes, and 32 (9.6%) with diabetes. Diagnosed patients were registered in a CHW patient log for follow-up, offered low-cost medications from CHW botiquines (community medicine chests), and counseled on appropriate lifestyle changes. While some had previous knowledge of their risk of diabetes and/or hypertension, the vast majority of patients were uncontrolled due to extensive barriers to health care access. These results underscore the prevalence of uncontrolled hypertension and diabetes in rural Guatemala and provide support for the novel use of CHWs as an intervention strategy in this setting.
Effect of MicroRNAs on KLF10-mediated Control of T Regulatory Cell Differentiation and Function

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CD4+CD25+ T regulatory cells (T regs) play a protective role in inflammation associated with atherosclerosis. KLF10 is an important modulator of T regs such that reduced expression results in decreased numbers and suppression function. Thus, determining the regulatory factors that tightly control KLF10 expression to modulate T regs is of great therapeutic interest. MicroRNAs (miRNA) regulate gene expression by imperfectly base-pairing at the 3’-UTRs of target mRNAs. In this project we hypothesized that microRNAs directly bind to the KLF10 3’-UTR to regulate KLF10 expression and affect T regulatory cell differentiation and function.

Using bioinformatic tools, we identified seven candidate miRNAs: miR-429, miR-425, miR-200b, miR-30b, miR-20a, miR-26a, miR-19a. Primary CD4+CD25- cells were isolated from mouse spleens and transfected with candidate miRNAs. Total RNA was isolated 24 hours after transfection and RT-qPCR was performed to measure KLF10 and Foxp3 mRNA. Transfection with 50 nM miR-26a and miR-30b each reduced KLF10 (0.61 fold in miR-26a, 0.84 fold in miR30b) and FoxP3 (0.57 fold in miR-26a, 0.59 fold in miR-30b) mRNA relative to NS controls.

HEK293 cells were co-transfected with miRNAs, KLF10 3’UTR, and pCMV-β-galactosidase plasmid. Luciferase assays were performed and normalized to total protein and β-galactosidase activity. Among the miRNA tested, miR-425 and miR-200b exhibited the greatest repression at 50 nM (fold change in luciferase/total protein compared to NS was 0.56 and 0.54 respectively.) At 100 nM, miR-26a repressed the KLF10 3’-UTR (fold change was 0.59 compared to NS).

Differentiation assays were performed by transfecting CD4+CD25- with 50 nM of miR-200b, miR-425, or miR-26a and allowing the cells to grow with IL-2. After 48 hours, cells were harvested, stained, and analyzed with FACS. Compared to NS controls, the fold changes in the ratio of CD4+CD25+/CD4+CD25- T cells were 0.88, 0.92, and 0.79 in samples transfected with miR-200b, miR-425, and miR-26a respectively.

Overall, miR-26a was shown to decrease KLF10 and Foxp3 mRNA and the proportion of differentiated CD4+CD25+ cells, but inhibition of the KLF10 3’UTR required higher concentrations. MiR-200b and miR-425 both repressed the KLF10 3’UTR and decreased the proportion of CD4+CD25+ cells, but did not reduce KLF10 mRNA. Taken together, these data suggest that miR-26a, miR-200b, and miR-425 may modulate KFL10 to control T reg differentiation although the consequences of this effect on suppressor function remain to be elucidated. Further work would include determining effects on KLF10/Foxp3 protein levels and ultimately the ability of miRNA-transfected T regs to affect inflammatory processes in atherosclerosis.
Investigating Breastfeeding and Weaning Practices in Urban and Rural Northern Vietnam

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Exclusive breastfeeding (EBF) is critical for an infant’s first six months of life because it provides the essential nutrients for growth and development as well as important natural antibodies to fight early sickness. Research indicates that EBF rates are poor in areas such as Vietnam thus contributing to the severe rates of childhood malnutrition in the country. Policies and interventions aimed at improving this problem should be tailored to current practices and knowledge gaps, which may differ by geography (ie. urban vs. rural). We, at the National Institute of Nutrition in Hanoi, Vietnam, proposed the following goals as a part of a larger study assessing timing of nutritional improvement for women before conception versus during pregnancy: 1) To assess trends in infant feeding practices through questionnaire-driven interviews; 2) To describe the feeding practices in a rural (Dieu Luong commune in Cam Khe district in Pho Thu province) and urban (Phuong Vinh Phuc commune in Ba Dinh district of Hanoi) area; 3) To test questions for future infant feeding questionnaires.

A total of 100 women with infants under one year of age were interviewed. Each interview was conducted in Vietnamese and involved a brief questionnaire and infant weighing.

The data concluded that in terms of breastfeeding practices, more mothers were able to breastfeed on the first day after birth in Phu Tho (78%) than Hanoi (66%). As for feeding trends and weaning practices, on average, mothers in Hanoi introduced supplementary foods about 4.5 weeks sooner than mothers in Phu Tho (11.5 vs. 15.9 weeks). Thus, mothers in Phu Tho had better EBF rates. As for nutritional content of supplementary foods, one difference was that mothers in Phu Tho used a little less commercially packaged powders in their porridge than in Hanoi. In terms of meat sources, lean pork was most commonly given in both communes. Beef and chicken were also given to infants; however, mothers in Phu Tho fed much less beef than in Hanoi. There was overlap in the types of fruits and vegetables infants in both communes were consuming, but there were also some differences. In terms of flavorings, twice as many mothers used soup-based powder to add to their meals in Phu Tho, while mothers in both places used fish sauce and gac oil. As for supplements, data from Phu Tho shows that mothers provided much less supplements than in Hanoi (20% vs. 62%).
Non-Melanoma Skin Cancer: Risk Factors and the System of Social Security and Health of Colombia

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In 1993 the passage of “Ley 100” in Colombia marked the beginning of a major transformation of the health care system from public provision of care to public supervision of a privatized system. Citizens are insured by one of two distinct mechanisms depending on their level of income with those in the “contributory” regimen paying into the pool for “subsidized” plans. While parity in coverage between these regimens was planned for the year 2000, thus far this gap remains. Currently, the Colombian government is investigating many of the largest insurance providers after an initial inquiry revealed inconsistencies in 75% of claims reviewed.

This study sought to elucidate the illness experiences of patients with non-melanoma skin cancers, diseases that are characterized by low mortality and, if appropriately and promptly treated, few complications. Though the study is ongoing, eleven patients have been interviewed multiple times using an open-ended in-depth approach.

Special attention was given to primary and secondary costs, legal tools utilized, and bureaucracy-imposed barriers. In addition to the help-seeking trajectories of patients, we attempted to characterize how this illness fit into a broader context of the patient’s life histories with a special interest in migration; family resources, connections, and priorities; intimate social networks; and the full range of suffering that has been experienced by all parties involved. Interviews were coded using inductively generated themes.

Already some themes of particular note have already begun to emerge. Bureaucratically imposed barriers have dramatically shaped patients’ access to care through a variety of strategies that include referrals to hospitals that do not provide needed services, referral to hospitals with whom the insurance company does not have a contract, failure to return calls of patients for weeks or months, and outright denial of coverage. One legal tool in particular, the “tutela” or writ of protection of constitutional rights, was sought by participants and was consistently sufficient to supersede any imposed barriers. Unnecessary medical complications due to these delays were common for patients despite coverage. Furthermore, these barriers necessitate enormous expenditures by patients and families on ancillary costs (transportation, food, accommodation) that most often far exceed the direct costs of treatment and may underlie a hidden discrepancy in expenditure between those in the contributory and subsidized regimens.

This study illustrates how government-regulated insurance plans in Colombia often fail to meet the health needs of those covered, the consequences of which are felt by the entire intimate social network of the patient.
Intellectual Disability Training in the Health Sciences: The European Perspective

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Intellectual disability (ID) has consequences throughout an individual’s lifespan, imposing a considerable burden on families and caregivers. It also requires high service provision and produces high health and societal costs. The interface between medical and neuropsychiatric aspects is highly complex in ID, making diagnosis more difficult than in other health conditions. Of course, a correct diagnosis is of paramount importance to providing the correct care. This reinforces the need for specific training in this specialist subject. ID is largely disregarded as a health issue by national and international organizations, and so is the case for training in ID and/or in the mental health aspects of ID (MH-ID), at every level of the education system (undergraduate, graduate and professional). Nowadays, the need for comprehensive information on MH-ID training policies and implementation is particularly relevant in Europe due to the recent process of harmonization, which has implications for training, mobility, and accreditation within the borders of the European Union. A proper understanding of the undergraduate, graduate, and professional education processes and strategies, as well as their impact on specific areas, is urgently needed in Europe, being particularly relevant in marginal areas with high societal impact such as training of MH-ID.

A search for literature relevant to intellectual disability training in the health profession was conducted of the following databases: Cochrane, Embase, PubMed, PsycInfo, and Science Direct. Only articles published after 1990 and based in Europe were included. In total, 114 articles that met all criteria were found. These articles, together with policy documents and information from key organizations in the field, will be used as the basis for a review of the development and availability of intellectual disability training for health professionals in Europe.
Medical Comorbidities of Homeless Individuals with and without Serious Mental Illness

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Homelessness is associated with increased severity of physical health problems as well as increased mortality. Serious mental illness (SMI) is also a risk factor for high-risk health behaviors, increased morbidity, and premature mortality. To our knowledge, no prior studies have examined the combination of homelessness and SMI as a compounded vulnerability for increased burden of illness. We hypothesize that homeless individuals with SMI will be more likely to have chronic medical conditions and substance abuse comorbidities than homeless persons without SMI.

We examined de-identified administrative data for all patients 18 years and older seen in a face-to-face visit at Boston Health Care for the Homeless Program between 1/1/2010 and 7/1/2010 and seen at least one year prior to 2010. We collected demographic information and ICD-9 diagnostic codes, which were used to identify twenty physical health comorbidities in addition to tobacco smoking, drug and alcohol use disorders. SMI was defined as having an ICD-9 diagnosis of schizophrenia, schizoaffective disorder, or bipolar disorder. To test our hypothesis, we conducted logistic regression analyses fitting multivariable models to examine the association between SMI and each health outcome, controlling for differences in age, race, sex, and duration of BHCHP clinical contact.

Of the 5,139 patients who met the inclusion criteria, 14.79% had diagnoses of SMI, including 2.74% with schizophrenia, 1.48% with schizoaffective disorder and 10.84% with bipolar disorder. Compared to those without SMI, patients with SMI were significantly younger, more likely to be female and white, non-Hispanic race and ethnicity. Individuals with SMI were more likely to be sleeping on the street or in housing versus in shelters. Individuals with SMI had significantly higher odds of having dental conditions (OR=1.343; 95% CI:1.093-1.649), COPD (OR=1.761; 95% CI:1.391-2.229), asthma (OR=1.773; 95%CI:1.442-2.181), hepatitis C (OR=1.634; 95% CI:1.360-1.964), traumatic brain injury (OR=1.985; 95% CI:1.372-2.872) and HIV/AIDS (OR=1.375; 95% CI:1.011-1.871). Overall, SMI was an independent predictor of having at least one of the selected medical comorbidities (OR=1.863; 95% CI:1.539-2.255). Patients with SMI were also more likely to smoke cigarettes (OR=1.26; 95% CI:1.07-1.49) and have drug (OR=1.852; 95% CI:1.58-2.17) or alcohol (OR=1.650; 95% CI:1.39-1.96) use disorders.

Homeless persons with SMI have a significantly higher burden of several medical illnesses and addictive comorbidities in comparison to homeless individuals without SMI. The excess burden of illnesses seen in homeless individuals with SMI reflects the global vulnerability of this population in addition to the adverse effects of substance abuse and other high-risk health behaviors.
An Ethnographic Study of Eating Behaviors, Food Security, and Obesity in
Preschool-aged Children in Santiago, Chile

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Background. Epidemic obesity is spreading to the developing world. Pediatric obesity is especially worrisome because it carries short-term educational risk, medium term psychosocial risk, & medium & long-term health risk. In Chile, pediatric obesity in 6-year-old children has nearly tripled, from 7% in 1987 to 19.4% in 2006. Rates are higher among poor children. Few interventions anywhere have succeeded in stemming or reversing rising rates of child obesity, suggesting we lack understanding of factors driving the epidemic.

We conducted a substudy within a school-based intervention to explore child, family, and community factors which may contribute to the pediatric obesity epidemic, including children’s eating habits, parental eating and feeding behaviors, parental perception of nutrition, overweight and obesity and family food security.

Methods. We designed an ethnographic study to investigate the influence of nutrition and environment in lower socioeconomic sectors of Santiago on the current pediatric obesity epidemic. We designed a three-faceted approach, measuring daily food intake in classrooms, taking daily field-notes of classroom activities and attitudes, and administering a four-instrument interview with parents or guardians.

Preliminary Results. We observed 195 children in 6 classrooms over 7 weeks and conducted 89 parent interviews (46% of students). We had BMI data for 60% of families interviewed. 75% of parents of overweight children inaccurately reported their child as normal weight, while 13% of parents of normal-weight children provided inaccurate reports. By parent report, there were significant differences between eating behaviors of overweight and normal weight children, with overweight children scoring higher on enjoyment of food (overweight mean 3.96 and normal weight mean 3.01; p<0.005), emotional overeating (1.49 and 2.04, respectively; p<0.05), and food responsiveness (2.02 and 3.23; p<0.05). Also, families with overweight children experience more food security issues than families of normal weight children.

Conclusion. Among poor, urban 4- and 5-year-old children attending public preschool in Chile, overweight children showed higher measures of food-seeking behaviors and were more likely to experience food insecurity at home. Parents of these children perceived that their children were normal weight. These findings suggest that the processes that contribute to the pediatric obesity epidemic are more nuanced than simple “calories in-calories out/nutrition-physical activity” models, and involve interactions between family food insecurity, child food-seeking behaviors and parental perceptions of what weight is healthy for their child.
Genetic analysis of how Duffy antigen expression level affects erythrocyte susceptibility to vivax malaria infection

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My project is a genetic investigation of how Duffy antigen expression level alters an erythrocyte’s susceptibility to vivax malaria invasion. Epidemiological and clinical studies show that human populations with reduced Duffy antigen expression are less susceptible to vivax parasite infection, but the effect of Duffy antigen expression level on erythrocyte susceptibility to invasion has not been experimentally shown; mature erythrocytes, lacking nuclei, have been unable to be manipulated by conventional genetic techniques. Here, I am genetically manipulating erythrocytes to precisely and directly assay the effect of Duffy antigen expression level on erythrocyte susceptibility to vivax infection.

I hypothesize that higher expression of Duffy antigen in the erythrocyte membrane will make the erythrocyte more susceptible to parasite invasion. Using an experimental system developed by the Duraisingh Lab, I am transducing CD34+ hematopoietic stem cells with lentiviral vectors and culturing them to maturation. To vary Duffy antigen expression level, I cloned promoters of different strengths upstream of Duffy antigen cDNA in a lentiviral expression vector and moved them into CD34+ cells to yield erythrocyte variants with a range of Duffy antigen expression level. I am in the final stages of validating these constructs through viral titer assays and eGFP-tagged promoter activity, and validating the viability and Duffy antigen expression level of erythrocyte variants through growth and antibody binding assays. After validation, I will test the variants’ susceptibility to invasion by culturing them with parasite and measuring the percentage of them that become infected.

Future studies involving the modification of Duffy antigen on the erythrocyte cell surface potentially include mutagenesis assays for structural insights into the receptor or combinatorial co-expression of antigens to identify invasion co-receptors. Thus this transgenic expression system for Duffy antigen expression on erythrocytes, once validated, will be a helpful tool for elucidating this and other important receptors.
In Progress: Development of a Novel Intervention for Increasing Medication Adherence in Youth with HIV

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HIV is increasing in prevalence among youth in the United States. Without antiretroviral medications, HIV usually progresses to AIDS and is fatal. However, with good antiretroviral medication adherence, HIV is not expected to progress to AIDS, and life expectancy is not expected to be reduced. Medication adherence in youth is particularly suboptimal. We proposed the development of an intervention to be used in the future by medical providers to help increase medication adherence among HIV-infected youth based on one that has been effective in adults.

We conducted qualitative semi-structured interviews with HIV-infected youth, ages thirteen to twenty-four about facilitators of and obstacles to medication adherence. These interviews informed the adaptation of an existing intervention for adults for use with adolescents. An initial small randomized controlled trial with 40 youth is currently underway. The intervention will be modified based on participant feedback for testing in a larger-scale trial.
Superhydrophilllic Dental Implants- New Strategies for Stimulating Early Osseointegration

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In the United States, it is predicted that there will be approximately 38 million edentulous elderly adults by the year 2020. Accordingly, the quality of dental implants must continue to improve in order to last in a population with an increasing life expectancy.

The purpose of the study is to evaluate the osteointegration capacity of immediate-loaded hydrophilic and superhydrophilic treated dental implants when compared to control. In a triple blinded study, mini-pigs will be treated with the three different types of implants. Next, maxillary and mandibular tissue samples with implants will be prepared into individual resin-block samples. Once prepped, samples will be machined and processed into hard tissue histological slides.

After staining of samples, histomorphometry will be utilized to measure “Bone volume per tissue volume” (BV/TV) (expressed as a decimal value) and the “Bone-to-implant contact” (BIC). The two parameters of bone volume per tissue volume and bone-to-implant contact change will then be averaged. If results are normally distributed, analysis of variance (ANOVA) and post hoc t-test will be proposed for statistical analysis to quantitatively determine the magnitude of efficacy of the hydrophilic and superhydrophilic implants.

At the current time, study data is waiting to be unblinded. If hypotheses can be confirmed, this study has significant clinical implications. Currently, there are three approaches to loading an implant into bone: immediate, early, and delayed. These three approaches differ with regards to how long one lets the alveolar bone socket regenerate before the implant is placed. Accordingly, it is extremely pertinent that osseointegration occur within the alveolar bone socket as quick as possible, especially in instances of immediate implant loading. While other studies look at osseointegration weeks later, it is most important to look at osseointegration days after implantation as a measure of functional stability. Because of the original methods developed at the Karl Donath Laboratory, we are able to look at bone augmentation around the superhydrophilic implants at day 5, 10, and 15, something that is yet to be done. If it can be demonstrated that superhydrophilic implants have significantly more bone supporting the implant base within days of implantation, the turnover rate from time of procedure to implant use would be greatly increased.
Viability Study of Chondrocytes in Polyethylene Glycol Gel using Pig Articular Chondrocytes

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Cartilage is a fairly simple, but highly specialized and functional connective tissue that consists of chondrocytes embedded in a three-dimensional network composed of proteoglycans, collagen, and water. Unlike bone or skin, which has great regenerative capability, cartilage has no vascular network, and in turn has limited innate ability for repair or regeneration. Articular cartilage injury from trauma between joints often results in scar formation, which can therefore result in permanent loss of structure and function.

Current strategies to generate tissue for restoring injured joint surfaces have demonstrated some encouraging clinical results, but there is no evidence that the new tissue that forms is characteristic of normal articular cartilage or can integrate with the native matrix, suggesting they are not a long term solution. Therefore, a therapy that can grow synthetic cartilage that more closely resembles cartilage and integrates with the native tissue is desirable.

One such approach involves a biocompatible polyethylene glycol (PEG) scaffold seeded with articular chondrocytes – the PEG scaffold would provide a three-dimensional environment favorable for promoting chondrogenesis for joint surface repair. Before growing cartilage in a mouse model, however, our goal was to test whether chondrocytes seeded in a PEG gel would have sufficient viability to move forward with an animal model.

The gels required UV light exposure to polymerize and contained some cytotoxic components that could inflict cell death. Initial viability studies did indicate high levels (>80%) of cell death. While initially we thought adjusting polymerization components or UV light exposure would improve viability, it wasn’t until we changed the media components that the viability was sufficiently improved, to above 80%.

After ensuring satisfactory viability, the next step is to set up immunocompromised mice models. 1, 3, 6 and 12 week mouse models, in which PEG gels seeded with bovine articular chondrocytes are sown into the mouse’s back, will be tested for cartilage development. Histological studies, biomarkers and mechanical testing will be used to measure the development of synthetic cartilage.
Assessment of Platelet-Derived Growth Factor and Vascular Endothelial Growth Factor Stimulation of in-vivo Intramembranous Ossification

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Dental implants are gaining popularity as a restorative option for patients with missing teeth. However, with insufficient bone at the implantation site, bone must be regenerated prior to implant placement. Angiogenesis is imperative for bone growth because blood carries oxygen, nutrients, and cells to the developing site. Two factors associated with vascular and bone development are platelet-derived growth factor (PDGF) and vascular endothelial growth factor (VEGF). A mouse calvaria model was chosen because its bone develops through intramembranous ossification, similar to that in the human jaw. The primary aim of this study was to examine the efficacy of PDGF and VEGF in promoting intramembranous ossification in the mouse calvarium.

Wild type C57Bl/6 male mice between 4-6 weeks of age were randomly assigned to one of four study groups; five mice were in each of the groups treated with saline, rhPDGF-BB, and rhVEGF-A165, and three mice were administered recombinant human Bone Morphogenic Protein 2 (rhBMP-2). Treatment solutions were delivered by subcutaneous injections over the center of the right parietal bone, taking care not to damage the periosteum. Injections were performed every eight hours over five days in the same site. Intraperitoneal injections of Calcein, a fluorescent label for bone formation, were performed two days prior to the first calvaria injection and one day following the last injection. Two days after the final calcein injection, animals were euthanized with carbon dioxide. Whole calvariae were harvested, fixed, embedded in plastic, and then sectioned for histomorphometrical analysis. The distance between fluorescent calcein lines in the calvaria was measured, which corresponded to the thickness of new bone formation during the experimental time frame. Four sections of calvaria were analyzed in each mouse, and new bone development was documented.

The mean new bone generation in the control group (saline) was 14.10 μm, and in the positive control group (rhBMP-2) was 33.61 μm. The mean bone thickness in the VEGF group was 14.05 μm and in the PDGF group, 16.82 μm. The bone growth resulting from PDGF injections was statistically higher than that of the control group. The VEGF group did not demonstrate a statistically significant difference in bone growth. The bone development in the PDGF-BB and VEGF groups was decreased compared to the BMP-2 group.

The study concluded that PDGF-BB may be clinically beneficial for use in bone regeneration procedures. More experimental work is required in order to answer a variety of clinical and scientific questions.
Quantitative Polarized Light Microscopy of Mammalian Cochlear Sections

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For most people with hearing loss, the underlying pathology is not known because the human inner ear cannot be biopsied today without causing permanent deafness. Currently employed imaging modalities, including CT and MRI, do not provide sufficient spatial resolution to visualize cochlear microanatomy. Novel imaging modalities being developed for ultimate application in humans in vivo will require a full understanding of the optical properties of various cochlear structures. To gain insight into such optical properties, we have applied, for the first time, quantitative polarized light microscopy (qPLM) to murine cochlear cross-sections. We have focused on the mouse model because its cochlear anatomy and physiology is similar to that of humans, and many mouse models of human deafness are available to test the diagnostic power of our approach. Polarized light microscopy provides information on sample birefringence, a property of anisotropic materials to decompose light into two orthogonally polarized rays. Although polarized light microscopy has been used extensively to study birefringent biological materials, it has rarely been applied to the cochlea. qPLM, an enhanced technique that allows for quantitative determination of sample retardance, which is proportional to birefringence, and optic axis orientations, has never been applied to the cochlea.

We hypothesize that the main birefringent signal in the cochlea is due to collagen type II and myelin. Both collagen, which is the major fibrillar component of the inner ear, and myelin, which ensheathes primary auditory and vestibular neurons, are known to exhibit birefringence. Unstained mid-modiolar cochlear cross-sections from CBA/CaJ (n=3) and C57BL/6 (n=3) mice were imaged using qPLM, revealing intricately detailed networks of fiber tracts. The images will be used to catalogue the retardance of various cochlear structures across strains. In addition, cochlear cross-sections will be fluorescently labeled using antibodies to collagen type II and myelin basic protein to test our working hypothesis. Our data suggest that qPLM provides novel insight into the optical properties of unstained cochlear cross-sections, in addition to complementing information obtained from histologically stained sections examined with conventional light microscopy.
Assessment of Myocardial Viability by Cardiac Magnetic Resonance Imaging for Surgical Treatment of Ischemic Heart Disease

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Patients who suffer from ischemic cardiomyopathy are at elevated risk of cardiac mortality, but their outlook can be improved by several mechanisms when invasive coronary revascularization successfully restores blood flow to viable myocardium. Determination of myocardial viability using noninvasive imaging, therefore, is a critical step in deciding whether a patient is a good candidate for revascularization or not; however, an important prospective, long-term clinical trial showed that current assessment of myocardial viability with stress echocardiography and single-photon-emission computed tomography (SPECT) did not adequately provide guidance to performing invasive coronary revascularization that could result in patient survival benefit. Whether this finding is due to limitations in the concept of myocardial viability or the inability of these two imaging modalities in widespread clinical use to adequately assess viability is of clinical importance.

Cardiac magnetic resonance (CMR) imaging has excellent spatial resolution and tissue contrast in assessing myocardial physiology and thus has been proposed to assess myocardial viability more precisely than echocardiography or nuclear scintigraphy. The aim of this pilot study is to test the hypothesis if myocardial viability determined by CMR can guide coronary revascularization and associates with patient survival benefit. Patients who are deemed to have little to no viable myocardium will be used as a control group. Propensity scoring will be performed to minimize bias from treatment assignment of the groups.

We are conducting a retrospective cohort study of all patients who have had a CMR study for viability at Brigham and Women’s Hospital (BWH) since 2001. The study was approved by the Institutional Review Board at BWH. All patients have left ventricular ejection fractions (LVEF) <50%. Three parameters are being assessed to determine viability via each patient’s CMR study: global infarct size from late gadolinium enhancement (LGE), transmural extent of infarction from LGE, and regional wall motion abnormalities.

Our initial cohort size was approximately 200 patients. Along with one of my mentors, I helped to conceive of the project and assessed the aforementioned CMR parameters over the course of the summer for these 200 patients. This cohort size, however, is likely to be too small to show a differential survival benefit, and thus we hope to increase the power of our study by combining data from other CMR centers. Data collection will continue through spring 2012, with data analysis to follow.
A Qualitative Analysis of the Beliefs and Behaviors of Hygiene Practices Related to Water in the Rural Villages of the Mchinji District

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This project was a pilot study that analyzed the beliefs and behaviors associated with water in the villages of the Mchinji District in Malawi. We created crude maps outlining each of the villages, and we analyzed the dynamics behind water access, water usage, gender roles, and power structures within the villages of the Mchinji District. Because of the Ministry of Water and Development in Lilongwe does not have data on water in the Mchinji District, we hope this study can provide some data and help alleviate or improve the current water conditions in these villages through water intervention programs.

We sampled 8 different villages and created crude maps for each of the village on which we pinpointed the exact coordinates of the water sources, and we collected data through structured and semi-structured interviews with village members and through observations as we moved through the villages.

Based on the data we collected, the main water sources used are taps, boreholes, wells that either has a top-cover constructed or not, rivers, and “dambos” which are swamp areas outside the village that members use to dig to find water. It is apparent that overall women use water more than men, and they are the ones to get the water along with children for their households. Women tend to use more water because they bear the responsibility of domestic chores that involve the usage of water. For instance, women use water for cooking, drinking, showering, washing clothes/dishes, sweeping the house, and for re-cementing the floor of their house. While in most cases, men use water for shower, drinking, and making bricks.

Most of the village members seem to trust and prefer boreholes as their main source of water because they feel it is reliable and has high water pressure. The “dambos” areas are used only for when there is a water shortage, and this occurs when during the months of October-December, or when the original water source is broken, or when there is a high demand on the water source.

Finally, it is not clear whether there are power structures associated with water in the villages. It is likely that these water sources are constructed and placed either because the local government decided to place them there, or that it was the chief’s decision. Further studies analyzing community organization and structure in the villages may be helpful before beginning to create water intervention programs.
Characteristics of Cervical Metastasis in HPV-related Oropharyngeal Squamous Cell Carcinoma

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Infection by the human papillomavirus (HPV) is a risk factor for oropharyngeal squamous cell carcinoma (OPSCC), and a recent reviews of large clinical trials head and neck cancer treatment revealed that 63.8% of OPSCC cases were positive for HPV-DNA. The aim of this study was to better characterize regional metastatic disease in HPV-positive OPSCC. Retrospective review of patients with OPSCC treated with an upfront neck dissection prior to the use of chemotherapy or radiation therapy between December 2000 and December 2010 was undertaken. Because p16 expression is associated with HPV infection in OPSCC, cases positive for either HPV or p16 were considered HPV-related.

Review consisted of 47 patients with OPSCC with 19 confirmed cases of HPV-related OPSCC (14 tested positive for HPV, 12 tested positive for p16 expression, and 7 tested positive for both). 3 patients had non-HPV-related OPSCC (tested negative for either HPV or p16). The records of the remaining OPSCC cases did not contain data on HPV infection or p16 expression. The average metastasis size of HPV-related cases was 4.22 cm, compared to 2.23 cm for non-HPV-related OPSCC and 3.46 cm for all 47 cases of OPSCC. The average number of metastases identified in HPV-related cases was 2.2 positive nodes, compared to 6 positive nodes in non-HPV-related cases and 2.45 positive nodes in all cases. Extracapsular extension was identified in 4 of 19 HPV-related cases, compared to 1 of 3 non-HPV-related cases and 1 of 47 in all cases. 58% of patients with HPV-related OPSCC reported tobacco use, whereas 100% of non-HPV-related cases and 66% of all cases had tobacco exposure. T-stages of the HPV-related cases were: T1 - 13 cases, T2 - 2 cases, T3 - 3 cases. Tx - 1 case, compared to 2 T1 cases and 1 T1/2 case for non-HPV-related cases. N-stages of HPV-related cases were: N0 - 1 case, N1 - 2 cases, N2A - 7 cases, N2B - 4 cases, N2C - 2 cases, N2B/3 - 1 case, N3A - 1 case, Nx - 1 case. All non-HPV-related cases were N2B.

This review of HPV-related cases of OPSCC revealed that metastatic nodal size was relatively large, the number of nodal metastases was limited and the prevalence of extracapsular extension appear to be low for metastases of this size. The small sample size of non-HPV-related cases precluded the use of this group as a comparison group for statistical analysis. Tissue testing of the uncharacterized cases is needed to for robust statistical comparison and further characterization of the relationship between HPV/p16 and metastasis.
The Effect of Health Insurance Reform Laws on the Rate of Upper Extremity Elective Surgery

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Recent national health care reform laws include provisions to decrease the uninsured rate, create health insurance exchanges, and novel partially-subsidized health care plans, which will have broad-reaching effects on orthopedic practices. The purpose of this study was to determine effect of similar state laws in effect since 2007 on the rates of upper extremity elective surgery in a practice that has served the state following health care reform.

Over a 3.75 year period, 7577 patients diagnosed with upper extremity injuries were identified at a single institution. Their demographics, insurance status, and plan of care were reviewed. Insurance categories included government-subsidized health care plan (Commonwealth Care), private insurance, Workers’ Compensation, military-related (TriCare), Medicare, Medicaid (MassHealth), non-Commonwealth Care, other insured, and uninsured. After adjusting for age, gender, and diagnosis, the proportion of patients who underwent elective surgery was calculated for each type of insurance.

Of patients with private insurance, 22% underwent elective upper extremity surgery. The adjusted rates of elective upper extremity surgery were similar across most insurance categories, with higher rates of elective surgery in the Workers’ Compensation and TriCare categories compared to the Commonwealth Care category. The odds ratios for Workers’ Compensation and TriCare were 1.70 [95% CI 1.17-2.45], p=0.01; and 1.67 [1.07-2.61] p=0.02, respectively. Uninsured patients were as likely to undergo surgery as patients with Commonwealth Care.

In a population with near-universal health insurance, a government-run health insurance exchange, and novel government-subsidized managed-care plans, there were few insurance-based differences in rates of elective upper-extremity orthopedic surgery.
Scl and Notch act downstream of Hedgehog signaling to promote hematopoiesis from endothelial cells

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Adult hematopoietic cells transition through a hemogenic endothelial (HE) intermediate during embryo development, but the signaling pathways modulating this transition are incompletely characterized. Although the Hedgehog (Hh) pathway is hypothesized to play a role in patterning blood formation, early embryonic lethality of mice lacking Hedgehog signaling precludes such analysis. To determine a role for Hh signaling in HE patterning, we assessed the effect of altered Hh signaling in differentiating mouse embryonic stem cells (mESCs), cultured mouse embryos, and developing zebrafish embryos. In differentiating mESCs and mouse yolk sac cultures, addition of Indian Hh ligand (IHH) increased the number of CD41<sup>+</sup>c-Kit<sup>+</sup> hematopoietic progenitors, whereas chemical inhibition of Hh signaling led to a decrease without affecting primitive-streak mesoderm formation. In the setting of Hh inhibition, Notch induction rescued hemogenic VE-cadherin<sup>+</sup> cells, demonstrating that Notch expands HE. Scl/Tal1 (stem cell leukemia/ T-cell associated leukemia 1) induction rescued VE-cadherin<sup>−</sup>CD41<sup>+</sup> cells, demonstrating that Scl/Tal1 converts endothelial cells to hematopoietic tissue. Moreover, VE-cadherin<sup>−</sup> cells isolated from the mouse yolk sac or paraaortic splanchnopleura, when virally transduced with Notch signaling or Scl, had increased hematopoietic colony-forming activity. Finally, ectopic Notch or Scl induction in zebrafish embryos rescued the expression of the prototypical hemogenic endothelium marker Runx1 in the absence of Hh signalling. Together, our results reveal that the Hh-Notch-Scl axis promotes embryonic hematopoiesis through endothelial-to-hematopoietic transition.
A Study of Common Variation at the NPPA/B locus and the Natriuretic Peptide Response to Sodium Challenge

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High blood pressure (BP) is one of the most common causes of cardiovascular disease. Abnormal salt regulation by the renin-angiotensin-aldosterone system has been well studied, but the counterbalancing natriuretic peptide (NP) system has not. NPs are released in response to increased cardiac wall stress and can be classified into two major types: atrial natriuretic peptide (ANP) and B-type natriuretic peptide (BNP). It has been found that genetically higher NP levels, genetically determined, are associated with lower BP, suggesting that NP may be involved in a salt regulatory pathway to control BP.

We sought to test the hypothesis that NP plays a critical role in salt handling. Ten percent of the population has a high ANP genotype that results in a higher resting ANP level. If NP is involved in salt regulatory mechanisms, those with higher ANP genotype should have a larger difference in their ANP levels after salt loading compared to those with a lower ANP genotype. The study will compare 80 individuals with high or low ANP genotype to investigate whether differences in genetically determined ANP concentrations lead to differences in ANP increase after chronic and acute salt loading. The primary outcomes of this study are comparison of high and low genotype groups for the following measures: 1) differences in resting NT-proANP concentrations after one week of low salt (10 mEq/d) vs. high salt diet (200 mEq/d) 2) differences between the peak and baseline ANP concentrations following saline administration after low and high salt diet, respectively.

The preliminary data examined the effect of chronic salt diets on blood pressure, and timed urine sodium output on 23 subjects (mean age of 25, BMI = 23.2, systolic BP = 116±10.7, diastolic BP = 74.5±7.0, 22 males) who completed both standardized diets. A paired t-test demonstrated that the mean BPs on high and low salt diets were not significantly different. The mean timed urine sodium output after high salt diet (137.7 mmol/mL) was significantly less than the expected 180 mmol/mL. NT-proANP levels were higher after completion of a high salt diet compared to low (n=3).

The lack of detectable effect of dietary salt on blood pressure is possibly due to the small sample size or the possibility that healthy young adults are less susceptible to acute BP changes induced by salt. The urine sodium output after the high salt diet may be lower than expected possibly due to high exercise rates among young volunteers. In the winter, NT-proANP, ANP, renin, and aldosterone levels will be available for comparison for each subject after low and high salt diet completion.
Melanoma is a highly aggressive and often deadly form of skin cancer with few effective treatment options. The current standard of care, which involves surgical resection with consideration for adjuvant therapy, such as chemo- or immunotherapy, yields objective tumor responses of approximately 10 to 20% with uncommon sustained remissions. These largely inadequate therapies have led researchers to explore oncogene-targeted therapy which has illustrated greater success in the treatment of some cancers.

To date, the most promising of these selective inhibitors in melanoma is vemurafenib indicated for the 30 to 60% of patients harboring melanoma with the BRAF V600E mutation. In a phase 3 study, vemurafenib was associated with a 48% response rate in B-raf mutated melanoma; however, its profound effects were found to be only temporary, achieving a mean progression-free survival of only 5.3 months. The complete response rate was a mere 0.9% due to drug resistance and subsequent tumor regrowth. These mechanisms of resistance have yet to be fully understood.

This experiment studied the mechanisms of action and resistance of B-raf inhibitors via previously unobserved kinetic studies of cellular proliferation in vemurafenib-treated N-ras mutants, B-raf mutants, and wild-type melanoma cell lines, with the intent of identifying possible trends that could better predict drug effectiveness. Three N-ras mutated, four B-raf mutated, and three wild type lines were either treated with 3uM vemurafenib or left untreated and followed over the course of five days using the AlamarBlue Cell Viability Assay (Invitrogen).

Results show that melanoma cells harboring the V600E B-raf mutation experience the greatest suppression in overall growth, with a range of 62 to 82% growth inhibition on day 5. The N-ras mutated and wild type cell lines displayed a lesser degree of suppression, ranging from 5 to 46% inhibition. Analysis of the rate of growth showed that in B-raf lines, faster proliferation in untreated cells led to greater inhibition of growth, not increased cell senescence, by vemurafenib. Trends were less obvious in both the N-ras and wild type lines.

Preliminary results demonstrated several points including 1) within the B-raf lines, the faster the growth rate, the greater the growth inhibition, 2) contrary to current literature, non-B-raf-mutated lines were also subject to substantial growth inhibition by vemurafenib, and 3) vemurafenib may be cytostatic rather than cytotoxic. These observations demonstrate a need to explore other correlates (e.g. protein expression) between growth rate and inhibition in various melanoma cell lines that might be better indicators for drug effectiveness rather than genotyping.
Improving In-Hospital Care for Patients with Autism: A needs assessment survey

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Objective: Hospital admission can be particularly difficult for patients with Autism. We created the Autism Care Plan program for parents to document their child’s specific autism-related needs while in the hospital. The purpose of this study is to analyze the results of the Autism Care Plans to detail the in-hospital needs of patients with autism.

Methods: A survey was developed containing 18 questions in the following categories: expressive communication, receptive communication, and social/pragmatic issues. Study data were collected and managed using REDCap electronic data capture tools hosted at Massachusetts General Hospital. REDCap (Research Electronic Data Capture) is a secure, web-based application designed to support data capture for research studies, providing: 1) an intuitive interface for validated data entry; 2) audit trails for tracking data manipulation and export procedures; 3) automated export procedures for seamless data downloads to common statistical packages; and 4) procedures for importing data from external sources.

Results: Twenty-four parents filled out the survey. Mean patient age was 15.7-years-old. The most common preferred modes for communication with hospital staff were “spoken language” (50%) “pictures” (46%) and “electronic device” (38%). Only 38% of patients use “spoken language” to express pain, while 67% of patients indicated they expressed pain thru “crying/screaming”, and 33% of patients thru “aggression”. The most common concern for sensory sensitivity was “loud volume” (63%) followed by “unexpected noises” (42%). 13.6% of parents indicated that their child would be unable to tolerate wearing a hospital gown, while 45.5% would be unable to tolerate wearing a hospital I.D. bracelet on their wrists. The part of the physical exam most commonly reported as “intolerable” was the throat (26%), followed by the ears (17%) while use of the stethoscope, “belly exam” and “reflexes” are universally acceptable. 75% of parents indicated that access to music, puzzles and videos would be helpful should their child require hospitalization; other useful resources include an escort upon arrival (38%), low lighting (29%) and weighted blankets (17%). 58% of parents indicated concern about safety while in the hospital, with 42% reporting concern about “self-injurious behavior”.

Conclusion: Specific trends exist regarding the needs of patients with autism when in the hospital. An understanding of these needs may improve the in-hospital experience for these patients and their families.
Imaging of PARP1/2-overexpressing cancers with novel radiotracer 18F-AZD2281

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Poly(ADP-ribose)polymerase-1 and -2 (PARP1/2) are nuclear proteins that recognize sites of DNA damage and form large, branched chains of ADP-ribose on specific DNA-associated proteins such as histones and itself. Poly(ADP-ribose) chains disrupt protein function and recruit DNA repair machinery to sites of damage. Tumors with defects in homologous recombination pathways, including BRCA1- and BRCA2-deficient cancers, have been shown to be sensitive to inhibition of PARP1-mediated DNA repair with PARP1 inhibitors alone or in combination with DNA damaging agents (e.g. cis-[Cl2Pt(NH3)2]).

The Weissleder group has successfully synthesized fluorescent and radioactive derivatives of the PARP1/2 inhibitor AZD2281. I evaluated one such compound, AZD2281-BODIPY FL, for its potential utility in imaging small numbers of pancreatic ductal adenocarcinoma (PDAC) and ovarian cancer cells in vitro and in vivo. We hypothesize that tumors with high levels of PARP1/2 will have high signal-to-background ratios using fluorescent and radioactive AZD2281-based imaging agents in vitro and in vivo.

To test this hypothesis, a panel of pancreatic ductal adenocarcinoma and ovarian carcinoma cell lines were characterized by Western blot and immunocytochemistry for PARP1/2 expression. Cells were then treated with AZD2281-BODIPY FL, fixed, and stained with anti-PARP. Fluorescence at 515 nm (AZD2281-BODIPY FL) correlated with fluorescence at 670 nm (anti-PARP), indicating that PARP1/2 expression level is a determinant of fluorescent signal strength of AZD2281-BODIPY FL in vitro.

Four cell lines representing a range of PARP1 expression levels were then xenografted into Nu/Nu mice and the tumors grown. Three mice bearing four tumor types each were imaged with AZD2281-BODIPY FL, sacrificed, and their tumors excised for stand-alone imaging and Western blot. Tumor fluorescence at 515 nm correlated with tumor PARP1/2 expression determined by Western blot, indicating that PARP1/2 expression level is a determinant of fluorescent signal strength of AZD2281-BODIPY FL in vivo. Significantly more AZD2281-BODIPY FL accumulated in tumors than in control muscle tissue, providing useful signal-to-noise ratios for detecting PARP1/2-overexpressing cells in vivo.

These data indicate that AZD2281-BODIPY FL is a useful tool for imaging PARP1 both in vitro and in vivo. Detection of smaller numbers of tumor cells in vivo with AZD2281-based imaging agents has promising potential for improving cancer diagnostics and clinical observation of progression and treatment efficacy.
Impact of sleep deprivation on procedural memory formation

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Currently some 70 million people in the United States have a sleep problem. One-quarter of America’s adults, 47 million people, don’t get the minimum amount of sleep they say they need to be alert the next day. Effects of sleep loss on work performance may be costing U.S. employers some $18 billion in lost productivity. In addition to its effects in alertness and response time, sleep deprivation impairs the learning of new memories. Studies have shown that even a single night of sleep deprivation produces a significant deficit in hippocampal activity during memory encoding. It is not clear if this effect is due to the impairment of attentional processes, or neuroplastic mechanisms.

To answer this question, we focused on procedural memory formation. Procedural memory refers to the set of processes associated with experience leading to permanent changes in the capacity for producing skilled action. To ascertain skill acquisition, we used the Serial Reaction Time Task paradigm. The sequences presented in the SRTT were either high or low order. The order of the sequence refers to the complexity of the association between the different elements in the sequence; high order denotes a sequence with information that is more complex than pairwise associations. Interestingly, it is only high order sequence learning which requires the hippocampus. This is illustrated by the fact that amnesic patients learn low order associations normally, but struggle at learning high order associations in the SRTT task. Since sleep deprivation is known to affect hippocampal-dependent memory encoding we would expect to see a bigger impact on the hippocampal-dependent high order sequence learning.

To test this hypothesis, 12 patients were randomized into two groups: high order and low order sequence. Each group served as the other group’s control. Measures of their response times were taken at three time points (baseline, post sleep deprivation & recovery) and their learning score (LS) was calculated.

Even though statistical significance was not achieved, consistent trends emerged. At baseline and recovery there were similar LS both across and within groups. Following sleep deprivation, the high order group had a 45.4% decrease in LS while the low order group had a 2.96% increase.

These results indicate that sleep deprivation is having more impact on high order sequence learning. This differential effect suggests that sleep deprivation may be affecting neuroplastic mechanisms and not just impairing attention.
The Role of CD38, NAD Levels, and Sirtuins on Neuronal Cell Survival During Ischemia

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Sirtuins are a conserved family of NAD+ dependent deacetylases that have been shown to play important roles in metabolism, cell survival, cancer, aging, and caloric restriction-mediated longevity of organisms ranging from yeasts to humans. Greater activation of Sirtuins have been shown to be protective in heart and neural cells during ischemic attack. Many of the positive benefits of Sirtuins have been discovered via the usage of exogenous Sirtuin activators such as Resveratrol. Further manipulation of the Sirtuin pathway via small molecules for the purpose of protection against disease is an area of great interest.

Based on the dependence of Sirtuins on NAD, we hypothesized that reducing NAD degradation would activate the Sirtuins’ pathways. CD38, a membrane-bound protein that was originally discovered in macrophages but is now known to be in a variety of tissue, including heart, muscle, and neural cells, degrades NAD in the cell. Thus, an inhibitor of CD38 may activate Sirtuin pathways via an increase in NAD. We performed a broad screen of 83,000 small molecules taken from the Harvard Medical School small molecule library for CD38 inhibitory activity. We chose the three strongest, most consistent candidates. Apogenin, the strongest of the three, was validated in C2C12 cells as increasing NAD levels in a dose-dependent manner.

Next, we set up stroke-like conditions in which N2A cells were placed in glucose-free, growth factor-free, and essential amino acids-free medium then placed in a hypoxic chamber. At one hour, two hours, three hours, and four hours of ischemic conditions, there was no difference in the number of dead cells between those in ischemia and those in normoxia by means of trypan blue counting. Only after 12 hours of treatment did we find that there is a difference in dead cells (50% dead in hypoxic cells). When performing NAD assays, we found that short treatments of hypoxia actually increased levels of NAD compared to normal cells with and without addition of Apogenin.

Further experiments are needed to determine the time course of NAD levels during ischemia and whether Apogenin would improve cellular functions and survival by tapping into the Sirtuins protective effects.
Attachment, Cognition, and Borderline Personality Disorder (BPD)

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BPD is a prevalent and chronically disabling mental illness characterized by disturbances in affective regulation, behavioral control, and interpersonal functioning. Previous research studies have correlated BPD with preoccupied and fearful insecure attachment styles. One theoretical model proposed by Fonagy, et al. explains a mechanism by which insecure attachment develops into BPD, namely that insecure attachment contributes to a disturbance in mentalization, a social cognitive skill that allows one to understand the mental states in oneself and others. This research study investigates the associations among BPD, attachment, and deficits in cognition, using a neuropsychological battery of tests and the Adult Attachment Interview.

Subjects were recruited from the larger Family Study of Personality Traits and Their Relationship to Psychiatric Disorders and had completed the following diagnostic measures: Structured Clinical Interview for DSM-IV (SCID-I), the Revised Diagnostic Interview for Borderlines (DIB-R), and the Diagnostic Interview for DSM-IV Personality Disorders (DIPD-IV). Based on these diagnostic measures, the subjects (N=52) were assigned to either the BPD group (N=23) or the non-BPD comparison group (N=29). The BPD and non-BPD groups were matched in age, education, IQ, and SES, but they were significantly different in psychotropic medication use, illicit drug use, trauma, and comorbidities.

This study, which improves on previous investigations of attachment and cognition in BPD by using age, education, and IQ-matched subjects, has three main findings. First, consistent with previous investigations, BPD subjects were more preoccupied and fearful in attachment than non-BPD subjects. Clinically, this corresponds to the dependency/counterdependency conflicts and the angry/fearful stance characteristic of the interpersonal style seen in BPD. Second, the BPD subjects demonstrated worse performance on speeded processing tasks than non-BPD subjects, but otherwise, the two groups demonstrated similar performance on attention, executive function, and memory tasks. This differs from findings in previous reports that did not have education and IQ-matched subjects, which may have exaggerated differences in neuropsychological testing. Lastly, as expected, a number of capacities to be self-aware and mentalize internal states of self and others in the social cognitive battery differed between BPD and non-BPD subjects. The mindfulness capacity of acting with self-awareness appears to contribute most to the impact of social cognitive factors on BPD. These findings suggest that the therapeutic target of increasing self-awareness in BPD can largely influence diagnostic status. This supports the use of the evidence-based treatments for BPD, which are mostly psychotherapeutic and aim to increase self-awareness through either dynamic or skills-based techniques.
Rotational Thromboelastometry to Predict Intraoperative and Postoperative Bleeding in Cardiac Surgery

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Coagulopathy and massive bleeding are severe complications of cardiac surgery, particularly in procedures requiring prolonged cardiopulmonary bypass (CPB). There is huge variability in transfusion practices across hospitals and providers in cross-sectional studies. This variability may indicate unguided decision-making, perhaps due to lack of reliable, predictive laboratory testing of coagulopathy to guide transfusion practice.

Rotational thromboelastometry (ROTEM) measures multiple coagulation parameters and may provide value from its ease of use, rapid results and measurement of several steps in the coagulation pathway. Yet the predictive value and utility of ROTEM remains unclear. This study investigated ROTEM predictive value for chest tube drainage after cardiac surgery.

A total of 321 patients undergoing cardiac surgery involving CPB were enrolled. Patient data was obtained from medical records, including chest tube output (CTO) from post-CPB to the first 8 postoperative hours. Perioperative and postoperative blood samples were collected for ROTEM analysis. Three measures of CTO were used as the primary endpoints for assessing coagulopathy: (i) Linear CTO; (ii) CTO dichotomized at 600mL (75th percentile); (iii) CTO dichotomized at 910mL (90th percentile).

Clinical and hematological variables, excluding ROTEM data, that were significantly correlated (P<0.05) with linear CTO were included in a stepwise regression model (Model 1). An additional model that contained ROTEM variables in addition to the variables from Model 1 was created (Model 2). Significance was declared at P<0.0167 to account for the three CTO endpoints. Net reclassification index (NRI), a conservative comparison of model performance, was used to assess overall value of ROTEM data.

For linear CTO, ROTEM variables improved the model’s predictive ability (P<0.0001). For CTO dichotomized at 600mL (75th percentile), ROTEM did not improve the model’s predictive ability (P=0.03). For CTO dichotomized at 910mL (90th percentile), ROTEM did not improve the model’s predictive ability (P=0.23). NRI similarly indicated that ROTEM results did not improve overall classification of patients (P=0.12 for CTO≥600mL; P=0.08 for CTO≥910mL).

These results suggest that ROTEM data do not substantially improve a model’s ability to predict chest tube drainage, beyond commonly-used clinical and laboratory parameters. While several ROTEM parameters were individually associated with CTO, they did not significantly improve goodness of fit when added to statistical models comprised of only clinical and routine laboratory parameters. ROTEM does not appear to improve prediction of chest tube drainage after cardiac surgery involving CPB and may not be useful in guiding transfusion during cardiac surgery.
The Impact of EGFR Mutations on Outcomes in Patients with Early-Stage Resected Non-Small Cell Lung Cancers

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A subset of lung cancers appears to be associated with somatic mutations in epidermal growth factor receptor (EGFR). Specifically, studies have found that EGFR mutations are enriched in non-smoking lung cancer patients, as well as people of female gender and East Asian descent. The mutation status of lung cancer patients is potentially of great clinical importance, since it predicts the responsiveness of cancers to certain targeted therapies. Tyrosine kinase inhibitors (TKIs), such as erlotinib and gefitinib, have already been found to significantly improve survival in EGFR mutation-positive patients with advanced disease. However, while the importance of EGFR mutation status in late-stage cancer patients has been proven, the implications of EGFR mutation status in early stage cancer patients is still unclear. The aim of this study was to explore whether EGFR mutation status had an impact on long-term outcomes—specifically recurrence rate, progression to nodal disease, and overall survival—in patients with early-stage resected cancers.

Our patient population consisted of all individuals with early-stage resected lung adenocarcinomas presenting to Massachusetts General Hospital for either surgery or follow-up care. We divided patients into two groups based on their mutation status, which was assayed with the “SNaPshot assay.” This is a multiplexed, PCR-based, comprehensive tumor genotyping assay performed on either formalin-fixed, paraffin-embedded, unstained slides, or fresh snap frozen biopsy. We further sorted patients into subgroups based on the type of resection they received (lobectomy, segmentectomy, pneumonectomy, or wedge resection). Finally, within each subgroup, we compared the mutant and non-mutant groups for rates of recurrence, progression to nodal disease, and overall survival using Kaplan-Meier survival curves.

Our study comprised a total of 296 patients, 46 harboring the EGFR mutation and 250 wild type. The two groups were comparable in terms of median age, ethnicity, pack-year smoking history, and co-morbidities. Our preliminary analyses indicate no significant difference in recurrence rate between groups. In patients with lobectomies, 5.6% of mutants experienced recurrences, compared with 6.3% in wild-type. Overall survival was 100% in mutants compared to 97.5% in wild-type. This difference was non-significant (p = 0.33).

These data indicate that EGFR mutants and wild-type patients do not have a significantly different in recurrence rates, progression to nodal disease, or overall survival. Moreover, the overall low rates of recurrence and death in both groups speak to the success of resection as curative treatment for early-stage lung cancer.
Fetal Growth and Anthropometrics in Relation to Serial Maternal Angiogenic Factors PlGF and sFlt-1

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Concentrations of the angiogenic markers placental growth factor (PlGF) and the soluble fms-like tyrosine kinase-1 (sFlt-1) vary greatly between otherwise normal pregnancies. The concentrations of the markers are most extreme in conditions of aberrant placentation including preeclampsia. We hypothesize that 1) even absent the effect of preeclampsia, decreased PlGF and increased sFlt concentrations are associated with reduced fetal growth and 2) this reduction is specifically manifested in reduced limb and truncal but not reduced head growth.

Singleton pregnancies (N=865) were prospectively followed with sequential blood sampling (at 10, 18, 24, and 35 weeks) and 3rd trimester fetal ultrasound measurements. PlGF and sFlt-1 levels were measured with the Abbott Architect assay. Gestational age specific Z-scores were evaluated for birth weight, abdominal circumference, femur length, and biparietal diameter.

PlGF and sFlt-1 levels at weeks 10 and 18 were not associated with birth weight or fetal anthropometric Z-scores. At weeks 24 and 35, PlGF was positively and sFlt-1 was negatively associated with birth weight Z-score. At these gestations, the angiogenic markers were associated with abdominal circumference and femur length but not biparietal diameter Z-scores. Linear regression, controlling for clinical covariates including the diagnosis of preeclampsia and using birth weight, abdominal circumference, and femur length Z-scores as the dependent variables, demonstrated independent effects of PlGF and sFlt-1 concentrations (R²=0.09, p<0.0001 for all).

Associations between the angiogenic markers and reduced fetal growth manifest in the 3rd trimester. Extreme concentrations of sFlt-1 and PlGF were associated with reduced limb and truncal but not reduced head growth.
Validation of Two Novel Monitoring Devices to Measure Physical Activity in Healthy Women

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Background: Measurement of non-exercise activity is proving increasingly important in health research. We sought to determine the accuracy and sensitivity to non-exercise activity of three activity monitors worn simultaneously by healthy adult women participating in a structured activity protocol.

Methods: Ten normal-weight women wore the Intelligent Device for Energy Expenditure and Activity (IDEEA; MiniSun, Fresno, CA), the SmartShoe, and the SenseWear Armband (SWA; BodyMedia, Inc.), during a series of activities that included standing, sitting still, sitting and fidgeting, lying down, and walking at varying speeds. Percentage of time postures were correctly identified was determined for the IDEEA and the SmartShoe, and activity counts collected from all three devices were compared.

Results show high accuracy in posture detection for both the IDEEA and the SmartShoe (97.4% and 94.2% accuracy, respectively). The SmartShoe showed superior sensitivity to movement while seated (“fidgeting”) compared with the IDEEA (p=0.004 and 0.049 difference between postures, respectively); all three devices distinguished between fast and slow walking.

Conclusions: Data support the ability of the IDEEA and the SmartShoe to recognize basic postures in healthy normal-weight women, as well as to detect movement within the seated position, i.e., “fidgeting.” These results thus support use of both devices in future research investigating non-exercise activity in women’s health.
Diffusion Tensor Tractography Reveals Impaired Language Pathways in Tuberous Sclerosis Complex Patients with Autism

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Tuberous sclerosis complex (TSC) is an autosomal dominant neurocutaneous disease caused by loss of the \textit{TSC1} (encoding hamartin) or \textit{TSC2} (encoding tuberin) genes. Neurologic symptoms are common and varied in TSC and include epilepsy and behavioral conditions like autism spectrum disorders (ASD). Between 17 and 61% of children with TSC exhibit ASD symptoms.

The purpose of this study was to investigate a potential correlate of poor neurological outcome in TSC by assessing the integrity of brain language pathways and their relationship to autism spectrum disorders (ASD).

42 patients with TSC and 42 age-matched control subjects were scanned with advanced diffusion-weighted MRI. White matter language pathways were identified with a validated automatic method and analyzed for microstructural characteristics, including fractional anisotropy (FA) and mean diffusivity (MD). Well-defined white matter pathways in the brain are characterized by high FA, as well as low MD. During normal development, brain white matter pathways increase in FA and decrease in MD.

Out of 42 patients with TSC, 12 had ASD (29%). After controlling for age, TSC patients without ASD showed a small decrease in FA compared to control subjects in all three language pathways examined; TSC patients with ASD had much lower FA than control subjects in all three pathways. Similarly, while TSC patients without ASD had only a small increase in MD compared to control subjects in the three language pathways, TSC patients with ASD had much higher MD than control subjects.

It remains unclear why some patients with TSC develop ASD, while others have better language outcomes. Our results suggest that aberrant development of language pathways may act as a marker for poor neurological outcome in TSC patients. The impaired microstructure in language pathways of TSC patients may be responsible for the development of ASD, although prospective studies examining the development of language pathways and subsequent ASD diagnosis in this patient population remain essential. Early diagnosis of ASD is crucial for improving the outcomes of affected children.
Real-Time Optical Frequency Domain Angiography Using Highly Parallel Graphics Processors

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Optical frequency domain imaging (OFDI) is a novel, FDA-approved optical imaging modality that has opened up the possibility of performing high-resolution (~10µm) intracoronary microscopy (a virtual biopsy) in living patients in the catheterization lab. An extension of OFDI, called optical frequency domain angiography (OFDA), enables flow-sensitive angiographic imaging and has been applied to the imaging of tumor angiogenesis in vivo. However, at current data acquisition rates, the OFDI system can only process ~10% of the acquired data in real-time on latest-generation, state-of-the-art processors. This is particularly burdensome in angiographic imaging, which acquires much larger datasets and requires extensive processing. As a result, the current system uses expensive high-throughput storage devices to store the raw imaging data and necessitates lengthy post-processing.

Despite the numerous potential applications enabled by a real-time 3-D visualization interface, such a real-time framework has not been implemented due to its high computational complexity requiring expensive computing infrastructure. Recent studies suggest that a graphics processing unit (GPU), which is a low-cost, yet very powerful computational platform with many parallel processors, is a potentially useful platform for OFDA-related processing tasks. Furthermore, since the GPU is designed for highly parallelizable tasks such as image processing, we hypothesized that a GPU-based implementation of the image processing tasks required in OFDA could provide sufficient acceleration for real-time 3-D visualization.

Here, we present a novel computational framework that performs real-time angiographic image processing using a GPU. The processing steps in OFDA have been accelerated by creating highly parallel GPU software. A general-purpose GPU programming language called CUDA C/C++ was used and the GPU algorithm was tested on a GPU with 512 parallel processing cores. The current GPU code can process data at a frame rate (~100 frames per second or 100 fps) much greater than the raw data acquisition rate (~10-20 fps depending on imaging settings). This opens up the possibility of incorporating more sophisticated image processing capabilities into the OFDA system. For example, a new GPU-based post-processing algorithm was added to reconstruct a 2-D colorized projection image from the 3-D volumetric dataset. Finally, to highlight the utility of the GPU-based angiographic reconstruction framework, we imaged the tumor vasculature in the dorsal skin of a mouse with tumor cells. The results suggest the intriguing possibility of visualizing tumor angiogenesis at high-resolution in vivo without injecting any extrinsic contrast agents in real-time.
Identifying the Mediators of Resistance to Targeted Therapy in HER2-amplified Breast Cancer

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About 1 in 8 women (12%) in the United States will develop invasive breast cancer over the course of their lifetimes. Of those who are diagnosed and treated with breast cancer, about 40,000 die every year from metastasis. A specific receptor tyrosine kinase, HER2, is amplified and/or overexpressed in 25-30% of all breast cancers. Treatment advances has decreased the death rates over the last decade. The introduction of a monoclonal antibody against HER2 (trastuzumab) in metastatic cancer that overexpresses HER2 is associated with a significantly longer time to disease progression, a higher rate of response, and improved overall survival. However, patients with metastatic breast cancer almost always develop resistance to this antibody and suffer disease progression.

Because of the efficacy of targeting HER2 signaling in HER2-positive breast cancers, we aim to circumvent the resistance problem encountered with anti-HER2 drugs. The type of resistance observed re-establishes downstream Ras/Erk and PI3K/Akt signaling pathways of HER2 receptor tyrosine kinase. We hypothesize that in HER2-amplified cells, there exists a unique dependence on specific molecular pathways, different from those of normal cells, that mediate the resistance to anti-HER2 therapies.

One approach to identify such unique pathway is to screen all the kinases in cancer signaling pathways. A recently documented screening method is to overexpress a library of kinases and kinase-related open reading frames (ORF) to identify genes that are important in driving drug resistance. It was shown that COT protein, one of the kinases, was found to be associated with de novo resistance to RAF inhibition in B-RAF positive malignant melanoma cancer cell lines.

In this study we use a similar screening approach to identify mediators of resistance to anti-HER2 targeted therapy by expressing over 600 kinase and kinase-related open reading frames (ORF) in an array format. Several dozens of ORF candidates induced resistance to anti-HER2 drugs in HER2+ breast cancer cell lines. We studied in depth on the molecular mechanism by which one of the ORF candidates, PRKACA, causes resistance to anti-HER2 drugs. We argue that a comprehensive understanding of resistance mechanisms in HER2-amplified cancers will lead to the development more effective treatment options available for all patients with this disease.
The Development of a Clinico-Social Model for Women’s Health in Zwedru, Liberia

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Nearly eight years ago, Liberia ended a fourteen year civil war that displaced over half of the population, killed a devastating number of people, and destroyed the country’s infrastructure. While the conflict left the country in a dire situation, it provided the women of Liberia, victims of the war and among the most vulnerable populations, a chance to re-conceptualize gender roles and become active participants in social and political life. Women were uniquely instrumental in organizing peace movements to both end the war and have since become increasingly involved as leaders in their community and government.

Despite the recent changes, Liberian woman continue to suffer from one of the highest maternal mortality rates in the world, poor access to health care, limited economic and educational opportunities, and a weak public services. They not only experience great gender inequity but their families and children also bear the consequences – thus magnifying the effects.

While there are numerous women’s rights programs, few integrate a multifaceted approach to development that links clinical care for critical health issues with job training and education. The purpose of this project was to develop an outline for an integrated Community Women’s Health Initiative that can best be implemented in Zwedru, a rural community in southeastern Liberia. Through Tiyatien Health, a local non-governmental health organization, this project focused on mapping the delivery of social and clinical services, identifying the prevalent issues women face, and outlining how health and economic services can be delivered. Previous efforts to integrate these programs for women have resulted in low loss to patient follow-up and the subsequent development of several education and economic empowerment programs. This suggests that a model that tightly integrates the clinical and social experiences of individuals can enable programs to holistically and effectively address the issues of women.

Preliminary work on this initiative has focused on several key areas. First, a strategic plan for the development of this program was created. This plan outlines the key components of the program and how it will be implemented. Second, a small cohort of women were mobilized to design the women’s health curriculum and to interface with the clinical services offered through Tiyatien Health. Third, a process for monitoring and evaluation was begun. While the program is in its nascent phase, it is being built as a scaleable model of clinico-social care that can prevent the fragmentation of crucial services in a rural, resource-limited setting.
Cardiomyocyte-specific knockout of the TRPM7 ion-channel leads to cardiomyopathy and conduction abnormalities

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The Transient-Receptor-Potential-Melastatin-Like-7 (TRPM7) ion-channel is an intra-membrane protein with selectivity for divalent ions – Zn\(^{2+}\), Mg\(^{2+}\), and Ca\(^{2+}\). The C-terminus of this protein is an \(\alpha\)-kinase which has been shown to phosphorylate cytoskeletal proteins, and is also postulated to regulate gene transcription. TRPM7 channel current is strongly inhibited by cytoplasmic Mg\(^{2+}\) ions and is also regulated by ATP, suggesting a function in Mg\(^{2+}\) homeostasis or cellular energy sensing. Furthermore, TRPM7 expression is ubiquitous; knockout mice lacking TRPM7 at both alleles do not survive past E6.5.

The first tissues to show robust TRPM7 expression during embryonic development are those of the cardiac lineage. We therefore used a Cre-lox system driven by cardiomyocyte-specific promoters to restrict TRPM7 deletion to cardiac muscle. Deletion driven by the \(\alpha\)-myosin-heavy chain gene produced a sporadic phenotype of severe dilated cardiomyopathy in approximately 25% of mice. This frequency was higher (~50%) in a heterozygous knockout background. Ejection fraction and fractional shortening were significantly reduced, and left ventricular mass was significantly elevated in these animals. Cardiomyopathy was often accompanied by severe conduction abnormalities, such as AV-nodal block, bundle branch block, and sinus node dysfunction. Both the dilated cardiomyopathy and conduction abnormalities were observed in mice as early as 3.5 weeks postnatal, and neither were elicited by Mg\(^{2+}\) deprivation (0.003 % Mg\(^{2+}\) diet), or banding of the ascending aorta. To investigate non-Mg\(^{2+}\) regulation of TRPM7, whole cell patch clamp recordings of HEK-293 cells over-expressing the channel by Zn\(^{2+}\) ions. Zn\(^{2+}\)-inhibited TRPM7 with a similar potency to that of Mg\(^{2+}\) (IC\(_{50}\)\(_{\text{Zn}^{2+}}\) = 575\(\mu\)M; IC\(_{50}\)\(_{\text{Mg}^{2+}}\) = 720\(\mu\)M).

Earlier cardiac-specific deletion of TRPM7 leads to failure of septation, in-utero congestive heart failure, and embryonic death. We observed significantly enhanced rates of apoptosis in the septum of these early knockouts. However, the cardiomyopathy observed in later-knockout mice (MHC-driven) was not associated with myocardial apoptosis.

These findings are in opposition to previous research suggesting that the dominant functions of TRPM7 are in Mg\(^{2+}\) homeostasis. Our results suggest that the observed cardiomyopathy and conduction abnormalities are the results of aberrant development due to disruption of TRPM7 channel function, or kinase function (or both) during embryogenesis. Interference with TRPM7 function may affect multiple distinct developmental processes to cause severe cardiovascular phenotypes.
Outcomes of Stenting for Stenosis of Intracardiac Lateral Tunnel Fontan Pathways

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A modified Fontan operation, in which systemic venous blood return is directed to the pulmonary arterial circulation without an intervening ventricular pump, is the standard form of palliation for severe congenital heart disease not compatible with two ventricle physiology. Over the last 20 years, the intracardiac lateral tunnel (LT) method has been one of the most widely employed variants of the Fontan operation. In an LT operation, one wall of the systemic-to-pulmonary “tunnel” connection is comprised of native right atrium (RA), while the remainder of the circumference is comprised of a synthetic baffle that is sewn within the atrium.

While the LT operation has contributed to improved outcomes among patients undergoing a Fontan procedure, it can be associated with various morbidities. One such complication is development of narrowing (stenosis) within the LT. Causes of and treatments for LT stenosis have not been addressed extensively in the literature, but LT stenosis has been diagnosed and treated with percutaneous angiography and stent placement in patients at Children’s Hospital Boston.

To describe the morphology of stenotic LT lesions and assess the safety and efficacy of percutaneous stent placement as a treatment, we retrospectively examined electronic medical records and intraprocedural angiogram data from a cohort of 51 patients who received LT stents between 1999 and 2011. In this cohort, a total of 18 stents initially had a pressure gradient across the baffle stenosis, while 33 were stented because of angiographic and clinical factors. None had a residual gradient after stenting. Stenting improved angiographic stenosis in all patients, with a mean increase of 174% in LT minimum cross sectional area. Two stent-related adverse events (new baffle leak after stent deployment) were reported in this series.

In conclusion, LT stent placement may be a clinically useful option for many patients with LT stenosis given its ability to significantly improve tunnel diameter without a high risk for adverse events. More work is needed to elucidate the etiology of LT stenosis and find ways to prevent its development.
Factors Affecting Sunscreen Use and Sun Avoidance in a National Sample of Organ Transplant Recipients

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Objective: Organ transplant recipients have an increased risk of non-melanoma skin cancers (NMSC) due to immunosuppressive therapy following transplantation. Use of sunscreen can help to reduce this risk. To inform strategies to increase sunscreen use, this study sought to identify patient and healthcare factors associated with sun protective behaviors by organ transplant recipients after transplantation.

Design: Cross-sectional retrospective survey about sunscreen use and sun avoidance behaviors before and after transplantation.


Patients: One hundred and ninety eight patients with no prior diagnosis of skin cancer.

Main Outcome Measures: Sunscreen use and other sun protective behaviors before and after transplantation. Frequency of sunscreen use and sun exposure was obtained by self-report on Likert scales ranging from never to always, and these responses were converted to a numerical scale from 0 to 4.

Results: Overall sunscreen use increased after transplantation (from 1.4 to 2.1, p< 0.001). Sex, Fitzpatrick skin type, receiving advice to avoid sun from a health care provider, and pre-transplantation sunscreen use were significantly associated with frequency of post-transplantation sunscreen use in multivariate models. Pre-transplantation sun exposure, advice to avoid sun, and pre-transplantation sunscreen use were significantly associated with sun avoidance post-transplant.

Conclusions: Both patient features and clinician advice are associated with sun protective behaviors after organ transplantation. These results help physicians target expanded sun protection counseling to those patients most in need of such intervention.
Social Consequences of U.S. Deportations and Return Migration for Honduras, Central America

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International migration is a facet of life for many Hondurans. Nearly 850 thousand Hondurans (11% of the population) live in the United States and over 15% of families residing in Honduras have at least one emigrant relative. Over the past eight years, deportations of Hondurans from the United States have nearly tripled, with 22,520 Hondurans deported in 2010. These deportations affect the lives of many Hondurans, including migrants and their families.

Research studies in El Salvador and Guatemala have demonstrated specific ways deportation can impact the health and well being of Central Americans, including disruption of family ties and elevated levels of stress. These findings provide important insights for policy makers, academics, and civil society organizations that are considering how to best respond to increasing levels of deportations. Nevertheless, there has been relatively little data on the social impacts of deportations specific to Honduras.

This pilot study aimed to develop an initial characterization of the impact of US deportations on Honduran families and communities. Qualitative interviews were carried out with 11 deportees, 11 of their family members, and 6 local institutions (i.e. police, health services, schools) at the field location of El Progreso, Honduras. The interviews focused on the experience of deportee reintegration and were facilitated through collaboration with a local community organization.

Preliminary coding and analysis identified a number of challenges that deportees face when attempting to reintegrate into Honduran society. Deportees note difficulty adjusting to changes in climate, culture, and quality of life. Only 2 of the 11 interviewees had steady, full-time work. Nearly all (10 of 11) hope to return to the United States. While most family members interviewed stated that the deportation of their loved-ones has brought them positive benefits of family unity, the majority (8 of 11) also pointed to the interrupted flow of remittances from their family member as a significant financial stressor. Leaders from local institutions stated that deportations lead to primarily negative consequences for the community, including neighborhood violence, gang activity, petty theft, household poverty, and interruption of academic studies.

Interview data will be further analyzed as part of an umbrella project sponsored by the Lonzano Long Institute of Latin American Studies at University of Texas, Austin. This larger project, which includes additional field locations and a larger sample size, aims to describe a more comprehensive picture of the social consequences of deportation in Honduras, El Salvador, and Mexico.
Cervical cancer accounts for 33.4% of all cancer cases among black women in Zimbabwe. Less than 5% of Zimbabwean women at risk of developing cervical cancer are ever screened in their lifetime, even though the basic infrastructure to perform exfoliative cervical cytology screening is in place.

The slow progression of cervical cancer from normal cervical tissue to invasive cancer is very important as it provides opportunities for prevention, early detection and treatment. A retrospective review of cancer of the cervix patients treated at Parirenyatwa Radiotherapy Centre (PHRTC) in Harare showed that 96.5% of patients presented with stage II and above disease, compared to 90% early stage one and below disease presentation in the developed world. Early stage disease has better survival outcomes and more treatment options.

Furthermore, the HPV vaccine for prevention of cervical cancer is yet to be registered and introduced in Zimbabwe, unlike in her neighbouring countries where it is already registered. The impact after introduction will be felt approximately in 20 or more years. This leaves the option of finding out what influences stage at presentation in the immediate future to influence intervention.

An analytic cross-sectional study on all new patients with invasive carcinoma of the cervix referred to Parirenyatwa Radiotherapy Centre was supposed to be carried out this summer by Dr Nyakabau. My objectives for the summer were to participate in the cross-sectional study through administering questionnaires to 50 newly diagnosed cervical cancer patients, to supplement quantitative data with qualitative data on the knowledge and attitude of health workers by carrying out at least 6 key informant interviews, and to expand on the current cross-sectional study by identifying at least 3 patients who have been previously diagnosed with cervical cancer but did not seek treatment so as to understand the cost and time required to get to a screening/treatment site.

However, due to complications in obtaining ethics approval from Parirenyatwa Hospital, I then switched to a qualitative approach and carried out semi-structured interviews in order to understand access to cancer care. Barriers that arose included financial barriers; lack of adequate public funds for screening, diagnosis and treatment since immediate public health priorities infectious diseases; lack of standardized management protocols; poor documentation and follow-up data; and lack of human resources (there are only 5 oncologists in the country).
Variability in MRI vs. Ultrasound Measures of Prostate Volume and Its Impact on Treatment Recommendations for Favorable-Risk Prostate Cancer Patients

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Physicians depend on radiographic estimations of prostate volume to determine whether patients qualify for brachytherapy (desired size $\geq 20\text{mL}$ and $\leq 60\text{mL}$) or active surveillance (desired PSA density $\leq 0.15$). Prostate volume can be determined from ultrasound or MRI, and further understanding of the concordance between these two measures is needed. The purpose of this study was to analyze variability in prostate volume as determined by contoured axial ultrasound slices, ultrasound ellipsoid (Height x Width x Length) calculations, and endorectal coil MRI (erMRI) ellipsoid calculations. The study also aimed to quantify the impact of variability in estimated volume on treatment recommendations for men with favorable-risk prostate cancer.

The study examined 72 patients who presented consecutively for consideration of brachytherapy for favorable-risk prostate cancer who had 3 volume estimates from direct contouring on ultrasound axial slices (2.5mm thickness), the ultrasound ellipsoid method, and the erMRI ellipsoid method.

Average gland size by the contoured ultrasound, ellipsoid ultrasound, and erMRI methods were 34.22, 37.15, and 39.58 mLs, respectively. All pairwise comparisons between methods were significant (all $p<0.02$).

Of the 68 patients who anatomically qualified for brachytherapy on ellipsoid ultrasound measures (size $\geq 20\text{mL}$ and $\leq 60\text{mL}$), 22 (32.35%) would have been disqualified based on either erMRI (5 patients <20 mL, 11 patients >60 mL) or contoured ultrasound measures (7 patients <20 mL, 3 patients >60 mL).

40 patients (55.56%) would be considered very low risk (PSA density $\leq 0.15$ ng/dl) based on calculations using ellipsoid ultrasound volumes, while 35 (48.61%) and 39 patients (54.17%) would be considered very low risk, and hence potential candidates for active surveillance, using contoured ultrasound and erMRI ellipsoid volumes, respectively.

The ultrasound ellipsoid and erMRI ellipsoid methods appeared to overestimate ultrasound contoured volume by an average of 8.56% and 15.65% respectively. In quantifying the impact of variability in volume estimates on treatment recommendations for favorable-risk prostate cancer, the study found that 32.35% of those who qualified for brachytherapy based on ellipsoid ultrasound volume would be disqualified based on ultrasound contoured and/or erMRI volume. As treatment recommendations increasingly depend on estimates of prostate volume, clinicians will need to take into account the method by which volume was estimated.
Socio-Demographic Profile and Clinical Presentation of Breast Cancer Patients in Rwanda

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Anecdotal evidence from Rwandan clinics point to rising breast cancer rates, yet very little is known about prevalence and epidemiology of the disease in Rwanda.

The aim of this study is to investigate the prevalence of breast cancer in Rwanda and describe socio-demographic profile and clinical presentation of patients treated for breast cancer at the three major Rwandese teaching hospitals.

We conducted a retrospective review of patients with breast cancer treated at Central University Teaching Hospital, Kigali (CHUK), Central University Teaching Hospital, Butare (CHUB) and King Faisal Hospital (KFH). Records from operating theatre log entries, admission registries, pathology reports and patient charts were included in the sample.

A total of 145 patients were hospitalized for breast tumors between January 2007 and May 2011. 40% of cases were seen at KFH, 29% at CHUK, 23% at CHUB and 12% at various district hospitals. Almost all patients were female (141 out 145). Average age of patients was 48.5 years (SD, 14), with a range of 15 to 89, and a mode interval of 41-50 years (32%). Out of 59 patients with residence data, 55 (95%) were rural. All patients who listed professions patients were farmers; n=25. Patients had an average of 6 completed births (SD, 2.8); n=20. Delay in patient presentation (defined as months of evolution of tumor mass until clinical intervention) was 25 months (SD, 39.5); n = 40. 23% of patients underwent mastectomy, 14% received chemotherapy and 10% lumpectomy. All chemotherapy was administered at KFH. The rest received other non-documented surgical interventions.

This descriptive study is the first attempt at characterizing breast cancer in Rwanda. We hope these finding will help spur and inform future studies.
Supporting PAHO’s Oral Health Program Activities on Developing Training Materials for the Oral Health Module

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The Caries Free Communities Initiative (CFCI) is an eight-year plan representing the sustained efforts to reduce the amount of caries in the ‘Regions of the Americas’ by 2015 by implementing strategies for improving oral health. The target population of these regions is the low socio-economic groups that include geographically isolated populations, women, children, and people infected with HIV. One of the main goals of this plan is to integrate oral health care into primary health care settings. The aim is to grant more access to information about recognition, prevention, and treatment of oral diseases.

The project set to accomplish this goal by using a ‘Train-the-Trainer’ methodology to empower dentists to go into target communities and give primary care workers the skills and confidence needed to prevent, diagnose and treat oral diseases at the community level. By doing so, primary health care workers will be better equipped to recognize and treat less complicated oral diseases, and know when to refer more complicated ones.

The project incorporated the successful strategies of marketing employed by the private sector as well as the successful strategies of using a problem-based learning approach.

The program consists of two workshops: a one-day workshop training dentists on how to train the primary health care workers, and a three-day work shop to train primary health care workers to recognize and treat oral diseases. The three-day training workshop consists of five interactive learning sessions, with each learning session having a pre-assessment quiz, tutorial case, lecture and review of a tutorial case, and a post assessment quiz. In addition, the learning sessions are complimented with five lectures that covered various topics such as fluoride varnish application and breast and bottle-feeding technique for children with cleft lip and palate.

A first draft of this program has been completed and will go through more phases of revision and evaluation before being implemented. When the workshop is finalized, it will be tested in real scenarios in two countries. From there, it will be scaled up to other countries in the Region of the Americas.
Tracheoesophageal Puncture for Voice Restoration: Retrospective Chart Review of All Cases at MEEI, 2000-2011

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Over 136,000 people will be diagnosed with laryngeal cancer this year worldwide. Although treatment modalities have evolved over the last decade, with disease control and organ preservation being achieved in the majority of cases, a significant number of patients will still require complete removal of the voice box for disease control. Loss of functional voice is a profound negative side effect of this potentially curative procedure. The tracheoesophageal puncture (TEP) voice restoration technique was introduced to restore voice in patients who have undergone total laryngectomy. In this technique, a prosthesis, acting as a one-way valve, allows air flow from the trachea to the esophagus, allowing speech production. This technique also has undergone evolution since its introduction.

We hypothesized that patients who undergo total laryngectomy with TEP and prosthesis placement in the same operation have improved outcomes compared to patients who underwent the more traditional approach, involving multiple procedures. To address this hypothesis, our project aimed to catalogue the histories of all patients at the Massachusetts Eye and Ear Infirmary who underwent TEP from January 1, 2000 to July 11, 2011 in order to determine which approach to TEP and voice prosthesis provides the best results. Our monetary search strategy returned 1096 patients between the dates of interest. Review of these patients yielded 111 patients who have had TEP at MEEI since January 2000. Fields of interest include time to voice acquisition, short-term and long-term complications, and 6-month and 12-month costs. Data extraction is currently underway. Results from this study may impact and inform future efforts at voice restoration for patients who have had laryngectomy.
Exploring Harvard School of Dental Medicine
Global Health Curriculum Opportunities in Ecuador

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A customized global health framework must be created within the specific context of a dental school educational system. To address the academic challenge of equipping dental students with the skill-set to address the prevalent chronic condition of oral disease on a public health scale, the Harvard School of Dental Medicine (HSDM) is seeking educational models to integrate into a global health curriculum.

To assist HSDM in collecting information to design a global health curriculum that includes the collaboration and exchange of knowledge among dental students/faculty at global sites. Information collected from this study will assist HSDM in refining the school’s vision for global health and improve the coordination of future outreach programs and curricular offerings.

This investigation included semi-structured interviews of approximately 30 minute duration with students/faculty from Universidad Cristiana Latinoamericana Escuela de Odontologia (UCL) in Quito, Ecuador to determine how to best enhance further collaboration as a model for future global health outreach programs and curricular offerings.

A standard set of questions was used to guide discussion and informed consent was requested prior to participation in the interviews. A total of ten participants were involved in this study, of which six were faculty from UCL and four were students. Post-survey debriefing was conducted in order to determine clarity of the questions and in order to obtain a measure of validity. Qualitative data was collated and results summarized.

Increasing resources for student education in the setting of an institutional financial deficit, improving research opportunities, and increasing infection control are UCL’s main university goals, as determined through administrative/student interviews. Program strengths of the dental school include the tremendous amount of clinical experience through a multitude of public health opportunities, leading to increased global health competency.

As part of the development of this curriculum, HSDM would greatly benefit from partnering with UCL as a global collaboration site. With an academic mission and strong dedication toward public service, the faculty and students of UCL can play a critical role in the establishment of HSDM’s first global exchange program.

Advances in healthcare are dependent on the quality of the workforce propagated by professional leadership within the healthcare system. The creation of HSDM’s global health curriculum must include partnerships with global academic institutions such as UCL. Assessment of the needs or demands of dental students and the educational deficits or potential benefits involved in this global health education must be evaluated.
We investigated the results of photoselective vaporization of the prostate using the 120W GreenLight™ High Performance System (HPS-PVP) for treating men with benign prostate hyperplasia (BPH) at 3 years follow-up. Medical records of 68 men who underwent HPS-PVP and were followed up for 3 years were retrospectively analyzed. Patients were older than 50 years of age with prostate volume > 30 mL, IPSS ≥ 8, maximum flow rate (Qmax) < 15mL/sec, and bladder outlet obstruction (BOO) index ≥ 20 noted on urodynamic studies. All operations were done by a single surgeon, and parameters including IPSS, Qmax, and complications were measured at baseline and at 6, 12, 24, and 36 months postoperatively. Patients who improved by at least 30% from baseline parameters were considered responders, and logistic regression analysis was done to determine predictors of response.

Mean age of patients was 71.6 ± 7.3 years, and mean prostate volume was 50.0 ± 17.0 mL. Mean IPSS and Qmax were 21.7 ± 7.9 and 8.7 ± 3.1 mL/sec, respectively. Average operative time was 60.6 ± 31.9 min, and 4 cases (5.9%) required urethral catheter insertion due to postoperative voiding difficulty. At 6 months follow-up, 50 (73.5%) patients responded to surgery with respect to IPSS and QoL score, and 40 (58.8%) maintained improvements up to 3 years postoperatively. Analysis of predictors of response at 3 years follow-up showed that at scores 19 or greater, the higher the IPSS; the greater the functional bladder capacity (FBC); the lower the frequency of nocturia; for bladder contractility index (BCI) ≥ 40, the higher the BCI the better the response.

HPS-PVP is a safe and effective surgical operation for the treatment of BPH, having demonstrated that 60% of patients maintained efficacy at 3 years postoperatively. Baseline IPSS, FBC, nocturia, BOO index, and BCI were valuable tools for predicting response to surgery.
Cancers are characterized by a resistance to apoptosis that enables survival in spite of the stresses of aberrant cellular processes. Previous work by our lab has demonstrated pro-apoptotic BH3-domain peptides can be used to determine the susceptibility of mitochondria to apoptotic signaling. This method characterizes how “primed” the mitochondria of a given tissue are for apoptosis and which anti-apoptotic proteins, if any, the cell is dependent on. Work from our lab shows high levels of priming correlate with increased sensitivity to chemotherapies. In fact, priming can be used to predict clinical response to chemotherapy. Recent work in this laboratory has indicated that malignancies are more primed than corresponding healthy tissues. By understanding what causes, modulates, and correlates with apoptotic priming we can better design and tailor anti-cancer therapies. The purpose of this study is to determine the effect of specific molecular oncogenic alterations on healthy tissue—how these changes correlate with chemosensitivity and priming.

Based on these prior findings, we hypothesized that genetic abnormalities common to many cancers might alter priming, corresponding to changes in chemosensitivity. We used two primary cell models: kidney epithelial and foreskin fibroblast cells, using electroporation to transflect PCDNA3 vectors with relevant oncogenes (Myc, Her2Neu). Additionally, primary human bronchial epithelial cell lines from collaborators were studied. These cell lines were immortalized with CDK4 and hTERT. They also had stably expressed malignant mutations in the p53 gene, Ras, and EGFR. Mitochondrial depolarization for priming was measured using JC1 dye, while cell viability after chemotherapy was measured using the Cell Titer Glo assay.

No changes in priming or chemosensitivity were observed with the HFF cells when transfected with Myc or Her2. The HBEC cells, however, showed differences in both priming and chemosensitivity. It was found that a kRas mutation decreased priming, and increased chemoresistance to a variety of chemotherapies. Similarly, preliminary data indicates that p53 knockout also decreases priming and increases chemoresistance. Additionally, the preliminary data suggests that hTERT decreases priming, even though it immortalizes the cells and increases proliferation. The chemosensitivity of the hTERT mutated cells corresponds to the decreased priming, not increased proliferation.

The data suggest that priming and chemosensitivity are closely linked, and that apoptotic priming may be a better indicator of chemosensitivity than proliferation. It also suggests a mechanism by which cancers manage to survive in spite of the stresses of increased proliferation and metabolism: some neoplastic genetic alterations also decrease priming.
Identification of genes regulating hematopoietic stem cell homing

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Hematopoietic stem cell transplantation (SCT) is a life-saving treatment option for patients with hematologic diseases. Hematopoietic stem cells (HSCs) for transplantation can be obtained through bone marrow aspiration or, in a process not requiring general anesthesia or hospital admission, via administration of growth factors, such as granulocyte-macrophage colony stimulating factor (GM-CSF), that promote egress of HSCs from the bone marrow. The cells are then harvested from the donor’s peripheral blood via venous access, and are infused intravenously into the recipient, allowing for the cells to circulate in the recipient bloodstream until engrafting in their bone marrow. SCT requires large numbers of donor cells (3x10⁶/kg of CD34+ cells) and therefore some patients cannot undergo autologous SCT due to too few cells. Also, some unrelated donors are unwilling to undergo the extensive harvesting necessary to acquire the necessary cell numbers. Finally, sources such as umbilical cord blood do not generally contain sufficient cells for individuals >40kg. Therefore, HSC numbers are a limiting factor in SCT. Our goal is to overcome that limitation by making HSCs more efficient, increasing the engraftment of cells such that fewer will be needed for successful SCT.

Based on studies by others and the Scadden lab, we hypothesized that the known molecular regulators of HSC localization (CXCR4, VLA-4, PGE2R, CaSR, PSGL-1) do not fully capture the spectrum of molecules important for HSC homing and engraftment. Therefore, we seek to identify novel candidate genes involved in HSC homing based on genetic evaluation of cells selected according to their in vivo localization.

HSCs were isolated from murine bone marrow and purified via lineage depletion and FACS sorting. Purified HSCs were stained with DiD and injected intravenously in lethally irradiated mice. After 48 hours, DiD⁺ HSCs were isolated from the bone marrow and spleen of the transplanted mice. mRNA from these cells was reverse transcribed to cDNA, which was amplified by PCR and then in vitro transcribed to generate cRNA. The cRNA will be fragmented and hybridized for microarray analysis. Novel candidate genes that are differentially expressed between the bone marrow and spleen, potentially regulating HSC homing to sites in the bone marrow, will be studied further via in vitro lentiviral-mediated overexpression or knockdown experiments in HSCs in order to regulate their expression. These studies may provide clinically relevant insight into how stem cells home under physiologic conditions and how we might manipulate them to improve the efficiency of SCT.
Racial/Ethnic and Socio-Contextual Correlates of Chronic Sleep Curtailment in Childhood

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Curtailed sleep has been linked to adverse outcomes. No longitudinal studies have examined racial/ethnic differences in sleep duration across infancy to mid-childhood. Our objectives were to examine the association between race/ethnicity and sleep curtailment from 6 months to 7 years of age, and to determine the extent to which socioeconomic and contextual factors both explain racial/ethnic differences and are independently associated with sleep curtailment.

We studied 919 mother-infant pairs in Project Viva, a pre-birth cohort study. The main outcome was the child’s sleep curtailment score. Beginning at 6 months and yearly from 1 to 7 years of age, mothers reported their children’s total sleep duration in a 24-hour period. To create the score, we first derived each child’s average sleep duration at three time periods (6 months-2 years, 3-5 years, 6-7 years). Next we coded sleep duration at these time periods as follows: 6 months – 2 years, <12 h/d = 0 and ≥12 h/d = 1; 3-5 years, <10 h/d=0, 10-<11 h/d=1, and ≥11 h/d=2; and 6-7 years, <9 h/d=0, 9-<10 h/d=1, and ≥10 h/d=2. Next we summed the three sleep codes, with 0 indicating curtailed sleep at all three periods to 5 indicating never having curtailed sleep. We conducted multivariable linear regression modeling.

In this cohort, 73% of the children were white, 13% black, 6% Hispanic, and 6% Asian. The mean (median, SD) sleep score was 3.7 (4.0, 1.3). Adjusted for sex, black (β -1.12 [95% CI: -1.36, -0.87]), Hispanic (-0.60 [-0.95, -0.26]), and Asian (-0.58 [-0.93, -0.24]) children had lower sleep scores than white children. After adjusting for maternal education, age, marital status, smoking and depression during pregnancy; household income; child breastfeeding duration, TV viewing, and physical activity, these differences were attenuated for blacks (-0.63 [-0.90, -0.35]) and Hispanics (-0.31 [-0.67, 0.05]), but not for Asians (-0.67 [-1.01, -0.32]). Maternal depression during pregnancy (β -0.55), having less than a college degree (β -0.25), a household income <$40,000 (β -0.41); more hours/day of TV viewing (β -0.26) and having a TV in the child’s bedroom from 4 to 7 years of age (β -0.31) were also independently associated with lower child sleep scores.

These data suggest that sleep curtailment is more common among black, Hispanic, and Asian children than white children. Maternal depression and lower education, lower household income, more child TV viewing, and having a TV in the child’s bedroom were also independently associated with childhood sleep curtailment.
Association of Unmet Medical Need with Use of Preventive Care for Children with and without Special Health Care Needs

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Objectives: Children with special health care needs (CSHCN) have greater use of medical services but continue to have greater delayed or unmet medical need than their peers without disabilities. This study investigates the association of receipt of preventive care with delayed or unmet medical needs for children with and without special health care needs.

Methods: Cross-sectional analyses of the 2007 National Survey of Children’s Health were performed. Participants were stratified into three groups: children without special health care needs; children with emotional, developmental, or behavioral conditions; and all other CSHCN. The independent, dichotomous variable was the child’s use of preventive health care. The dependent, dichotomous variable was the child’s delayed or unmet medical need. Bivariate and multivariate logistic regressions were employed to determine odds ratios for delayed or unmet medical need according to the child’s utilization of preventive care.

Results: In the bivariate analyses, all children (OR=0.8); children without special health care needs (OR=0.8); and CSHCN with an emotional, developmental, or behavioral condition (OR=0.5) were less likely to experience a delayed or unmet medical need when utilizing preventive care compared with those who did not. In the multivariate analyses, only CSHCN with an emotional, developmental, or behavioral condition were less likely to experience a delayed or unmet medical need (OR=0.6) when utilizing preventive care compared with those who did not.

Conclusion: Delayed and unmet medical need for CSHCN with emotional, developmental, or behavioral conditions may be further reduced by ensuring their acquisition of preventive care, particularly within a medical home.
Thoracoabdominal Esophagectomy shows Improved Long-term Survival for Treating Adenocarcinoma of the Distal Esophagus and Esophagogastric Junction

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Surgical resection for esophageal cancer, especially via left thoracoabdominal esophagectomy, has historically poor outcomes. This has led to the impression that surgery is unsafe and ineffective. However, marked changes in the pattern of esophageal cancer suggest that these assumptions may no longer be valid. The current study aims to assess the modern outcomes of left thoracoabdominal esophagectomy for adenocarcinoma of the distal esophagus and esophagogastric junction (EGJ).

A retrospective cohort study was performed on 132 consecutive patients with adenocarcinoma, who underwent left thoracoabdominal esophagectomy at the Massachusetts General Hospital between 2002 and 2010. Operative measures, complications, indications for reoperation, in-hospital mortality, and 1-, 3-, and 5-year survival were assessed.

In-hospital mortality was 1.5%. An uncomplicated recovery occurred in 61.4% of patients, while 38.6% developed at least one postoperative complication. Atrial fibrillation was the most common complication, occurring in 27.3% of patients. There were 8 clinically significant anastomotic leaks (6.1%), for which 6 patients required reoperation. The 1-year, 3-year, and 5-year survival rates were 89.4%, 63.8%, and 59.4%, respectively.

The morbidity and mortality following left thoracoabdominal esophagectomy in this study was acceptably low and in many instances improved upon previous studies. Most notably, our 5-year survival rate of nearly 60% is the best reported for any therapy. These results offer great promise for the left thoracoabdominal approach in the modern era and suggest that surgeons should be familiar with its merits for treating adenocarcinoma of the distal esophagus and EGJ.
Near Infrared Fluorescent Imaging for Bladder Cancer Diagnosis and Treatment

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Each year in the United States over 70,000 people develop cancer of the urinary bladder and almost 15,000 die from their disease. More than 90 percent of these cancers are urothelial tumors (also called transitional cell carcinomas or TCCs). For a chance to avoid the disastrous outcomes of later-stage disease, it is imperative to diagnose and treat TCC as soon and as thoroughly as possible. Unfortunately, at the onset of symptoms, many patients have multiple tumors of varying size and with current treatment not all of the cancerous cells are necessarily removed, leading to high rates of recurrence, repeat procedures, and disease progression.

In order to facilitate the clear visualization and complete extraction of these tumors, we proposed the use of a fast acting and rapidly clearing near-infrared fluorescence (NIRF) agent that is preferentially cleaved into its active form by key mediators of tumor growth, matrix metalloproteinases (MMPs). This commercially available agent, MMPSense750TM (MMPSense), has been shown to be an effective imaging tool in a previous study of breast carcinoma. Here, we applied it to human xenografts of TCC in swine bladders.

We began by developing a robust system for ensuring survival of porcine bladder tissue ex vivo. The bladders were harvested within 30 minutes of sacrificing the animal. They were then sectioned into ~0.5 cm² pieces, stripped of outer connective tissue, and placed epithelial-side up on pre-cut sterile gelatin matrices in a 12-well dish. The wells were then filled to the level of the gel-tissue interface with a mixture of keratinocyte serum-free medium, recombinant epidermal growth factor, bovine pituitary extract, an antibacterial, and an antifungal. The media was changed every 2-3 days, and assessed for viability with an alamar blue assay at 7 and 14 days. Almost 80% of the samples (19 of 24) were still viable at 14 days post organ removal.

We then injected six samples (prepared as described above) with 0.1mL of solution containing five hundred thousand UMUC3 TCC cells and left to grow for three days. These samples were then instilled in MMPSense solution and viewed at 30 minute intervals for 3 hours, then again at 6, 12, and 24 hours. No difference in appearance was noted between these samples and those that had not been injected with TCC cells.

Future work will begin with increasing the fluorescent agent’s concentration, testing it on other cell lines, and pending success, moving to an in vivo model.
Melanoma, the most aggressive form of skin cancer, has recently demonstrated a worldwide increase in incidence. Search for novel therapies to improve patient outcomes has led to use of immunological approaches to treat malignant melanoma, such as vaccination with autologous tumor cells engineered to secrete GM-CSF (GVAX), as well as T-cell stimulating antibody therapies such as FDA-approved anti-CTLA 4 (ipilimumab). The success of certain immunological therapies has now ushered in a need to understand the components of successful and failed developments of immunologic tumor memory, as well as tumor escape from the same. We currently are treating a patient (K008) whose melanoma recently recurred after nearly two decades of control following GVAX therapy. This patient represents a unique opportunity to begin to identify the components of immunologic memory and escape with regard to tumor immunotherapy, which remain as of yet unstudied in this new era.

Our main objective was to utilize SEREX to identify protein antigens that have been relevant in recurrence of melanoma in a patient long after successful initial vaccine. Furthermore, we aimed to understand components of T and B cell memory as they relate to immunotherapy. Our final objective was to continue the search for novel protein antigens that can be used as targets in future immune based therapies.

We used serological analysis of recombinant cDNA expression libraries (SEREX) to screen a tumor cDNA phage expression library with patient’s sera to produce candidate antigenic targets that were subsequently sequenced. To date we used SEREX to screen K008 serum following the second round of successful immunotherapy for her recurrent melanoma. Serum was screened against the melanoma cDNA library created from K008’s original melanoma 2 decades ago. This afforded a unique opportunity to study antibody responses by a patient to her initial tumor following a recurrence.

Preliminary results have yielded 4 intracellular antigens that patient K008 has developed antibodies to following the anti-CTLA4 treatment for her recurrent melanoma: SETD2 (histone methyltransferase), SR-9G8 (splicing regulatory SR protein), DNA-PKc (DNA-dependent protein kinase catalytic subunit) and eEF1A (translation elongation factor 1a). These antigens are different from those found when SEREX was performed following successful treatment with GVAX for her initial tumor, implying a differential set of antigens involved in the “immunologic recurrence” or “immunologic control of recurrence” processes. Still to be performed are SEREX screening of sera from different time points, including time of recurrence but preceding treatment, as well as utilizing different screening techniques (such as protein array) to increase the yield of putative protein antigens.
Disparities among Patients Discharged with Pending Tests

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Patients are frequently discharged from care while the results of tests are pending. This may result in avoidable medical errors. Given known racial/ethnic disparities in health care delivery and outcomes, disparities may also exist in patients with tests pending at discharge (TPADs). Accurate description of the population discharged with TPADs is necessary in order to better target interventions and improve care.

The objectives of this study are: 1) To determine the proportion of tests pending among patients discharged from the hospital by demographic factors (race, insurance, income), 2) to determine the proportion of actionable test results finalized post-discharge among patients discharged from the hospital by demographic factors, and 3) to explore an association of demographic factors on appropriate follow-up of the results of actionable tests finalized post-discharge.

A retrospective cohort study patients discharged from medicine and medicine subspecialty services from September 2010 to March 22, 2011 at Brigham and Women’s Hospital was conducted. Univariate analysis of outcome variables was completed for patient race/ethnicity. Outcomes were compared between patient race/ethnicity utilizing Fisher’s Exact Test and ANOVA. Future analysis will utilize multivariable regression to include covariates and adjust for clustering within patients seen by the same provider.

Interim analysis included 260 patients. 15 patients were excluded for lack of racial/ethnic identification. Study sample included 126 (51%) men, 119 (49%) women; 44 (17%) Hispanic, 55 (21%) Black, 146 (56%) White; 127 (52%) Medicare, 44 (18%) Medicaid, 74 (30%) private/other. There were 1012 total TPADs (574 chem/hem, 109 path, 60 rad, 269 micro). 34 (13%) patients required a follow-up action. This analysis was underpowered (18%) for statistical significance, but some trends existed. Hispanics consistently represented the largest proportions of TPADs (66% chem/hem, 34% path, 23% rad) compared to blacks (64% chem/hem, 34% path, 23% rad) and whites (57% chem/hem, 27% path, 15% rad). Hispanics also had the highest overall mean number of TPADs (3.1), compared to blacks (2.7), and whites (2.6).

Many patients are discharged from care with TPADs. Preliminary findings suggest that Hispanic patients are being discharged with higher rates of pending tests than other groups. Further analysis must be done in order to explore whether disparities exist in rates of actionable TPADs and whether appropriate follow-up action is taken. Patients with TPADs must also be tracked for adverse events to determine clinical significance of pending tests at discharge. Corrective interventions should be considered pending relationship of TPADs to racial/ethnic disparities in health outcomes.
Addressing Rural Health Disparities in India with Mobile Phone Applications for Community Health Workers

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India has large discrepancies in quality of health care between rural and urban areas, and the use of mobile phones as tools to guide community health interventions has been identified as a way to help overcome challenges of rural health care delivery. The customizable platform CommCare, which can be installed on mobile phones and serve as a mobile primary care companion for rural community health workers (called ASHAs, or Accredited Social Health Activists, in India), shows unique potential in being able to address this discrepancy.

Through collaboration with the Boston-based software company Dimagi, the grassroots organization NEEDS in Jharkhand, and the Melghat Area Development Project of World Vision India in Maharashtra, I aimed to address local needs for safer pregnancies and improved immunization and nutritional status monitoring of children with CommCare. With NEEDS, I sought to scale up their use of a multimedia CommCare pregnancy checklist to 28 additional ASHAs, and with World Vision, I aimed to help design a CommCare application to assist ASHAs in collecting data on child health and delivering timed and targeted counseling to mothers.

I spent two and a half weeks on site with NEEDS, conducting focus groups and interviews with ASHAs to assess the strengths and weaknesses of CommCare and plan for an adequate CommCare scale up. I also spent two and a half weeks on site with World Vision, defining the application content, designing the application, and training 10 ASHAs to use the application. The remaining two weeks I spent planning logistics and working remotely on technical support from Delhi.

In this time, I successfully helped NEEDS iterate their CommCare pregnancy checklist and plan trainings for 28 additional ASHAs, as well as designed and implemented World Vision India’s first CommCare pilot. The NEEDS training dates are still pending, but the World Vision pilot has shown nearly 100 form submissions from the 10 ASHAs to date.

While progress has been slow on both projects since my departure, my work laid the foundation for these two organizations to utilize mobile technology to improve health care delivery in maternal and child health. Though these projects show potential in enabling ASHAs to better manage data and counsel mothers, continued monitoring of both projects will be necessary in order to assess the impact of this work.
Short-Term Exposure to Ambient Air Pollution and Blood Pressure in the Framingham Heart Study

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The association between exposure to ambient particulate matter (PM) air pollution and blood pressure (BP) is uncertain. We investigated the association between short-term average levels of PM$_{2.5}$ and black carbon (BC) and BP in the Framingham Heart Study (FHS) Offspring cohort, hypothesizing that higher short-term exposure would be associated with higher BP.

In a repeated measures prospective cohort study, systolic (SBP) and diastolic (DBP) BP and clinical and demographic information were obtained at the FHS Offspring Exams 7 (1998-2001; 1966 eligible participants [n]) and 8 (2005-2008; n=1604). PM$_{2.5}$ (mean daily level 9.9 µg/m$^3$) and BC (mean 0.84 µg/m$^3$) concentrations were measured at a central monitoring site near downtown Boston, Mass. Subjects living beyond 40 km from the monitor were excluded. We assessed the association between 1, 2, 3, 5, 7, 14, 21, and 28-day moving averages (MAs) of the pollutants’ concentrations and the BP outcomes. We used a linear mixed effects model with a random intercept for each subject to analyze the overall association between pollution exposure and BP measurements, adjusting for age, sex, body mass index, use of lipid-lowering and antihypertensive medications, diabetes, cardiovascular disease, smoking, apparent temperature, and date.

A 1 µg/m$^3$ higher 7 day MA of PM$_{2.5}$ was associated with a -0.010 (p=0.92) lower SBP and -0.078 (p=0.17) lower DBP. For BC, a 1 µg/m$^3$ higher 7 day MA was associated with a -0.23 (p=0.86) lower SBP and a -0.98 (p=0.18) lower DBP. Results for other MAs were similar.

In this cohort of largely suburban community-dwelling middle-aged-to-elderly white adults, there was no association between short-term exposure to PM$_{2.5}$ or BC and BP. Future analyses will incorporate additional FHS exams and more precise exposure assessments, as well as assess the association between chronic exposure to traffic related pollutants and BP.
Laminar Microelectrode Analysis of Seizure Onset and Spread in the Epileptic Human Cortex

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Epilepsy is a neurological disorder affecting over fifty million people worldwide; it is characterized by a predisposition to recurrent, unprovoked seizures. Despite the prevalence of this disorder, relatively little is known about the neurophysiological mechanisms underlying the seizures. With current treatments of epilepsy limited to antiepileptic drugs (AEDs) with many side effects, surgical resection with high risk, and devices that regularly deliver neural stimulation without feedback-based modulation of stimuli, it is clear that a more effective and safe treatment is necessary. The use of microphysiological along with macrophysiological approaches to characterize seizure activity will provide a more complete framework for understanding the electrophysiological mechanisms.

By combining intracranial EEG (iEEG) data with single-unit (neuron) or multi-unit (cortical column) activity microelectrode data, we expect to enhance our understanding of seizure initiation, propagation, termination, and localization. In particular, we hypothesized that laminar microelectrode recordings in humans would provide important physiological information that would allow us to recognize seizure onset before it appears on iEEG recordings, and to distinguish the seizure focus from areas outside the seizure focus. We expect that a comparison of pre-ictal data up to forty-five minutes before the seizure with interictal data will reveal microphysiological changes preceding the seizure.

We have obtained preliminary results from 39 seizures in 18 patients across 5 institutions. These data show promising deviations from baseline in the time leading up to seizure onset, as well as heterogeneity across the cortical layers. In addition, we have analyzed single unit neuronal information from 4 patients and find changes (both increases and decreases) in firing rates for individual neurons, which also precede the seizure. Preliminary analysis shows that these changes are rarely observed between seizures. Remarkably, these changes were present both near to and far from the seizure origin. Together, these results bolster support for the idea that there is a physiologically distinct pre-ictal period and call into question traditional ideas about the seizure focus. More practically, they suggest a new way forward in predicting, and eventually, controlling seizures.
Long-term Health Status and Quality of Life of Kidney Donors and Recipients

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Since Dr. Joseph Murray performed the first successful living donor kidney transplant at Brigham and Women's Hospital in 1954, living donor kidney donation has become the optimal treatment for patients with end-stage renal disease. Roughly half of all renal transplants performed in the USA in 2010 involved living donors.

There is a high burden of proof to demonstrate that kidney donation is safe. Donation has not been shown to cause progressive renal dysfunction; however, a small increase in blood pressure has been noted in donors. Donors have been shown to live longer than the general population and experience heightened quality of life. The health status of kidney transplant recipients decades after the procedure is also of great interest. Hypertension and cardiovascular issues are major causes of morbidity. The limited literature suggests that quality of life of recipients is comparable to that of the general population.

This ongoing study examines multiple outcomes of survival, renal function, hypertension, and quality of life in a unique historical cohort: the kidney donors and recipients involved in the earliest transplant operations performed by Dr. Murray at BWH. The twenty-seven identical twin donor-recipient pairs were identified using historical records, whose follow-up time post-transplant spans from 41 to 57 years. A questionnaire was developed to collect several data points: GFR, serum creatinine, blood pressure, and presence of ESRD or other morbidity. Questionnaires are currently being sent to subjects in addition to the SF-36 survey, an established tool measuring quality of life. We hypothesize that donors will exhibit normal renal function, slightly elevated blood pressure, and normal if not increased quality of life. We hypothesize that recipients will have GFR and serum creatinine within normal ranges or slightly elevated, be hypertensive, and experience normal quality of life.

With an approximate average follow-up of 50 years post-operation, this study can contribute significantly to current knowledge of the safety and effectiveness of renal transplantation in the long-term. In addition to being of unique historical interest, this study's cohort of identical twins presents an opportunity to study outcomes of transplantation without immunosuppression.
Physicians, payers and policymakers are interested in whether global payments—strategies that combine capitation incentives with pay-for-performance (P4P) bonuses—will contain healthcare spending and improve care quality. In 2009, Blue Cross Blue Shield of Massachusetts (BCBSMA) engaged 12 Physician Hospital Organizations (PHO) in a global payment model called the Alternative Quality Contract (AQC). However, the effect of such strategies on pediatrics may be limited because of its generally small proportion of PHO business.

The objective of this study is to characterize the size and nature of pediatric services within the 12 PHOs that engaged in BCBSMA’s AQC. Specifically, we examine: (1) the number and proportion of primary care physicians that are pediatric, (2) whether PHOs are affiliated with a hospital that provides a full range of inpatient pediatric services, and (3) the socioeconomic (SE) setting in which PHOs are located.

The structure of the study was cross-sectional and included 3 publicly available data sources: (1) physician directories available through each PHO website to determine physician number, type, and proportion pediatric; (2) Agency for Healthcare Research and Quality (AHRQ)’s Kids’ Inpatient Database - to determine the number and type of pediatric inpatient beds at each hospital, and (3) the U.S. Census Bureau’s 2000 Census - to characterize the SE setting of each PHO using an Area-Based Socioeconomic Measure (ABSM); MA mean is 0 (SD 10, Range -26 to +26). Physicians were considered “pediatric” if they were pediatricians or family practitioners.

Of the 10 PHOs that had pediatric providers, there were on average 79 pediatric providers (SD 53, Range 27-203), comprising 1.8-23.0% of the total primary care workforce within each PHO. Seven PHOs included hospitals with licensed pediatric beds; these had an average of 31 pediatric beds (SD 20, Range 16-59). Two PHOs were affiliated with hospitals that provided a full range of pediatric services (general and intensive care neonatal beds, general and intensive pediatric beds), while most others only had general neonatal and pediatric beds. On average, PHOs were located in SE settings slightly above average for the state, with 2 located in SE tracts more than 1 SD below state average; PHO ABSM mean 0.21 (SD 4.7, Range -9.44 to +5.31). PHOs with a larger proportion of pediatric providers and full inpatient services were dispersed among both high and low SE census tracts.

Pediatric providers and services comprise a small proportion of PHOs currently engaged in the AQC. It may be challenging for new payment models like the AQC to alter pediatric care quality and spending within large, mainly adult-oriented organizations.
Role of Vitamin D metabolism in the Pathophysiology of Rotator Cuff Arthropathy

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Recent evidence suggests that the prevalence of vitamin D deficiency, measured by serum 25-Hydroxyvitamin D (25-OHD) concentration (below 20 ng/ml), can reach an upwards of 93% in certain populations [3-6]. Research has shown that hip [9], vertebral, wrist, and proximal humerus fractures [10], osteomalacia [11], bone growth retardation [12], and skeletal deformities [12] are all directly and significantly associated with deficient levels of serum 25-OHD.

Further, evidence has demonstrated both the capability of human marrow stromal cells (hMSs) to metabolize vitamin D as well as its functional importance in maintaining bone health. This concept has been provided using hip and femoral bone marrow samples [20]. However, nothing has been shown with regards to shoulder tissue and disease.

Rotator Cuff Arthropathy (RCA) is a shoulder complication associated with a complete rupture of the cuff joint. It diagnostically manifests with leaking of the synovial fluid and alterations in the mechanical and nutritional state of the glenohumeral joint. In regards to its relationship with vitamin D, pilot studies have shown that RCA uniquely presents with diminished bone density, fatty infiltration of the shoulder muscle, and soft bone impression during surgery.

This project tests the hypothesis that vitamin D deficiency plays a significant role in the pathophysiology of these RCA manifestations. To test these hypotheses, human bone marrow from humeral head samples have been collected from post-surgical RCA and Osteoarthritis subjects (n=14). Undifferentiated, low-density marrow mononuclear cells were separated and enriched utilizing Ficoll/Hisopaque 1077 centrifugation from the humeral head bone samples. They were expanded in monolayer culture per protocol (Invitrogen, Carlsbad, CA). Total RNA has been isolated from the hMSCs using Trizol reagent (Invitrogen) and reverse transcribed into cDNA with SuperScript II (Invitrogen). To assess vitamin D status, primers for CYP27B1 and VDR will be used for amplification and analysis.

Blood chemistries were also obtained from RCA and OA subjects and were assessed for serum 25OHD and PTH levels (n=47). Further, MRI and CT images were acquired for these subjects (n=47) and analyzed for fatty infiltration and atrophy of the rotator cuff muscles (Supraspinatus, Infraspinatus, Subscapularis, Teres Minor) using Goutallier’s classification system.

We hypothesize that these data will provide greater understanding of the risk and pathophysiological manifestations of RCA. Compared to OA, we predict that RCA subjects will have significantly lower serum 25-OH levels, higher serum PTH levels, greater atrophy, higher fatty infiltration, and lower molecular expression levels of the enzyme CYP27B1 in hMCSs.
Duane’s syndrome (DS) is a congenital eye-movement disorder constituting up to 5% of strabismus cases, a prevalence of ~0.1% in the overall population. DS is characterized by an inability of the affected eye to abduct, adduct or to move in either direction. Absence of the corresponding abducens nerve has been shown to be the major cause of the DS phenotype. On attempted adduction of the affected eye, globe retraction is also commonly observed due to co-contraction of lateral and medial rectus muscles. This results from aberrant stimulation of the lateral rectus by misguided branches of the oculomotor nerve. There is no cure for DS; however, prism glasses or alignment surgery are options for symptom management.

Although most cases of DS are sporadic, an estimated 2-5% of patients show familial inheritance, most commonly segregating as a dominant trait. The Engle lab discovered the two DS genes reported to date, SALL4 and CHN1, using genetic linkage analyses of such families. Based on screens that showed the absence of SALL4 and CHN1 mutations among many other affected individuals and families, we hypothesized that a third disease gene could be located using DNA samples of a large, 3-generation family that segregated dominant for DS and did not harbor mutations in either gene.

To test this hypothesis, genome-wide Single Nucleotide Polymorphism (SNP) data was processed into SNP genotypes for thirteen family members. Next, a subset of representative, informative SNPs from the original marker set was isolated and used to run both two-point and multi-point linkage analyses to determine which markers were linked to the proposed disease locus. Using microsatellite markers, haplotypes were reconstructed and analyzed for inheritance.

By testing models under different penetrances, seven regions of linkage across six chromosomes were defined with maximum LOD scores of 1.55. Ultimately, the potential location of the disease allele was narrowed to a combined 2.7% of the genome containing 702 genes. Due to the large number of candidate genes, DNA samples from the two most distantly related affected family members were submitted for whole-exome sequencing.

These data continue to support the hypothesis that a novel genetic etiology of DS exists and can be identified within this family. Whole-exome sequencing can further assist in localizing a causative mutation, and subsequent characterization of the putative gene may elucidate a more comprehensive understanding of DS pathology.
The Effect of Massachusetts Health Reform on Emergency Department Utilization

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In 2006, Massachusetts passed legislation that established a near-universal level of health insurance in the state. The impact of these reforms on health care utilization, and emergency room visits for primary care treatable conditions in particular, is unclear. In this study, we used data on all emergency room visits in Massachusetts, Maryland, and New Jersey during the three-year period immediately before and after Massachusetts health care reform was implemented in 2006 to investigate the relationship between near-universal coverage and emergency department utilization. Using a difference-in-difference approach, we compared annual state-level ED visit rates for low-and high-severity conditions as well as overall utilization. As a secondary analysis, we compared state-level ED visit rates for several low-severity conditions that are generally amenable to primary care settings, including asthma, acute bronchitis, upper respiratory infections, lower respiratory diseases, and fluid and electrolyte disorders. The results of this study are still pending.
Magnetic Dragging of Blood Clots via Antibody Binding of Magnetic Nanoparticles

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Stroke, myocardial infarction and pulmonary emboli are major causes of death in the United States. These diseases may be caused by blood clots, which can lodge in critical arteries and cause ischemic damage. Clots can form in the arterial system, especially in the case of atherosclerosis, or in the venous system. When formed in arteries, clots consist mainly of platelets and fibrinogen and are called white blood clots. In contrast, red blood clots that form in the venous system consist mainly of erythrocytes trapped in a fibrinogen meshwork. The current methods of treatment for blood clots include surgical removal, systemic anticoagulant therapy and thrombolytic therapy.

This research focused on utilizing nanotechnology to develop a more targeted, less invasive method to remove red and white blood clots. The goal of this research was to attach magnetic nanoparticles to blood clots then use an external magnetic field to remove the clot via dragging. This study evaluated the effectiveness of different binding methods between the nanoparticle and red and white blood clots. The outcome was evaluated by measuring the maximum distance between the clot and external magnet that could be achieved before the clot no longer followed the external magnetic field.

For red blood clots, anti-fibrinogen antibodies were bound to magnetic particles to act as a bridge between the clot and magnetic particle. Four methods of binding magnetic particles to anti-fibrinogen antibodies were studied: binding through the terminal carboxyl group on the antibody, using an NHS-ester linker to bind the terminal carboxyl group on the antibody, using an NHS-ester linker to bind the antibody disulfide bond, and using electrostatic interaction between the NHS-ester linker and charged protein surface of the blood clot. Dragging experiments showed that binding the magnetic particle to the anti-fibrinogen antibody through the disulfide bond was the most effective method.

Research on white clots focused on methods to attach magnetic particles to the white blood clot. The binding experiments carried out were: hydrophobic binding, varying concentrations of anti-fibrinogen antibody bound magnetic particles, 1:1 mixture of magnetic particles with attached antibodies and magnetic particles with recombinant tissue plasminogen activator (rt-Pa) attached, and a 1:2 mixture of the same solution. Although microscopy verified that magnetic particles were attached to the white clot, dragging was unsuccessful. Further research is needed to understand why fewer magnetic particles bind to the white blood clot compared to the red clot and to develop binding methods that allow the red clot to be dragged over a greater distance.
The Antibacterial Effects of Orexin on Periodontal Pathogens in the Oral Cavity

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Chronic mild to moderate periodontitis affects the majority of adults, and 5-20% of adults are affected by generalized severe chronic periodontitis. There are more than 400 species that colonize the oral cavity, many of which have been associated with periodontitis, including Enterococcus faecalis, Fusobacterium nucleatum and Aggregatibacter actinomycetemcomitans. In response to periodontal pathogens, the host innate immune system produces antibacterial factors which involve small antimicrobial peptides (AMPs, MW<10 kD), such as LL-37 and human beta defensins (hBDs). LL-37 and hBDs have demonstrated in vitro bactericidal effects on a variety of periodontal pathogenic and cariogenic bacteria, including P. gingivalis, and S. mutans, as well as oral fungi such as Candida albicans. However, when a single species of AMP was assayed, the bactericidal effect mediated by either LL-37 or hBDs was found to be attenuated in the physiological concentration of salt. Therefore, only a low level of bactericidal effects could be expected by these AMPs in saliva and other microenvironments having a physiological concentration of salt.

Previous studies indicated that AMPs could work additively with specific neuropeptides such as Orexin (ORX) to mitigate the salt-sensitive bactericidal effect of LL-37 or hBDs on E. coli. Based on these data and others showing that ORX was found in the gingival crevicular fluid and saliva of the oral cavity, we hypothesized that Orexin, possesses antimicrobial activity against periodontal pathogens, especially by promoting additive bactericidal effects along with LL-37. To test this hypothesis, antibacterial activity was assessed for ORX alone and combined with LL-37 against F. nucleatum, E. faecalis and A. actinomycetemcomitans. Antibacterial activity was measured using ATP and bactericidal assays. Our preliminary results suggest that Orexin displays bactericidal activity against all three bacteria and that there is an additive effect of Orexin on the bactericidal activity of LL-37 resulting in up-regulation of the decreased bactericidal activity of LL-37 in the physiological concentration of salt.

This study has the potential to develop a novel therapeutic antibacterial regimen for oral infections. These results could lead to the development or identification of a drug or naturally occurring compound that increases Orexin in saliva and GCF without inducing inflammatory or unwanted side effects.
Assessing Pediatric Nutrition and Caretaker Knowledge through Feeding Practices in Shanxi, China

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In Traditional Chinese Medicine (TCM), “fire” or huo is a characteristic of the body that is believed to cause many negative symptoms. Chinese people do not consume large amounts of dairy products, which may be linked with beliefs in shanghuo. In China, the rate of rickets among children 12-24 months is reported conservatively around 3.7%. In 2003, Evergreen Health Services conducted a survey with 250 children in Shanxi Province, China and found that there were seasonal discrepancies in calcium levels due to the TCM beliefs in shanghuo.

This study explored if calcium intake differences were due to caregivers’ lack of education and/or beliefs in shanghuo and also looked at children’s food intake. 40 structured interviews with caregivers of children aged 17-52 months were performed regarding knowledge of calcium, belief in shanghuo, and a daily food intake survey focused on calcium-rich foods.

Caretakers had little knowledge about calcium; 75% of caretakers did not know what calcium was and when asked which foods were the best sources of calcium, answers were extremely varied. 31.4% of caretakers listed shanghuo as a reason to not give their child dairy products. Caretakers also had varied answers when asked how to test for a lack of calcium and how lack of calcium manifested itself. Children often consumed calcium products as part of their diet (80% dairy products, 15% soy products, 20% calcium supplementation). A food intake survey showed that children’s diets were nutritionally rich.

Despite Chinese beliefs that calcium intake may cause shanghuo, which are still prevalent, children in Shanxi Province, China, were found to be consuming adequate amounts of calcium and be nutritionally cared for overall. Caretakers in this area, however, had low knowledge about calcium and calcium-rich foods. Education is still needed in the area of health and child development, but this lack of knowledge is not translating to malnutrition in children of Shanxi Province, China.
Plasma, Not Platelets Induce Osteoblast Differentiation in Human Bone Marrow Stem Cells

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Platelets or thrombocytes are hematopoietic cells derived from the megakaryocyte precursor. While traditionally known for their role in hemostasis, they play many other functions. These functions are attributed largely to their growth factors, which include the platelet-derived growth factors, transforming growth factor-β, vascular endothelial growth factor and epithelial growth factor. When secreted, these factors modulate cell mitosis, collagen production, recruitment of cells to injury sites and inducing cell differentiation, which are all critical factors in wound healing. These pro-healing capabilities led researchers and oral surgeons to hypothesize that increasing platelet concentration at bone graft sites would increase growth factor concentration and facilitate early bone regeneration.

Oral surgeons have therefore used platelet-rich plasma, defined as highly concentrated human platelets in a small volume of plasma, in an attempt to improve the success of bone grafting. Current literature on the efficacy of this technique is conflicting. One possible reason for this conflicting data is that the techniques used to prepare the platelets differ between studies.

To better understand the importance of platelet isolation techniques, our lab has developed an in-vitro model to assess the role that platelets and their plasma individually and together have in osteoblast differentiation. Platelets were previously extracted from volunteer donors by standard aphaeresis procedures. The extracted platelets were activated by thrombin to secrete their growth factors prior to or after the removal of plasma. These preparations were called platelet-rich plasma supernatant (PRPS) and platelet released supernatant (PRS) respectively. Previously work in our group showed by alkaline phosphate assays in the MG63 human osteoblast cell line that PRPS and fresh frozen plasma supernatant (FFPS) both significantly increased osteoblast differentiation when compared to a serum free control (p<0.01), but PRS did not.

To confirm this in primary cells, human bone marrow stem cells were isolated and cultured from three patients. Platelet preparations from two donors were introduced to cells and thymidine-incorporation and alkaline phosphate assays were performed to study cell proliferation and osteoblast differentiation respectively. Thymidine-incorporation studies confirmed established literature that PRPS and PRS both increase proliferation, while FFPS did not. We then showed that PRPS and FFPS both stimulated alkaline phosphate activity while PRS did not. This data first confirms, in our in-vitro model, that osteoblast proliferation can be attributed to platelet factors, and is independent of serum. More importantly, this data suggests that osteoblast differentiation can be attributed specifically to plasma serum and not platelets themselves.
Predictors of Outcome for Patellar and Trochlear Osteochondritis Dissecans in a Pediatric Population

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Osteochondritis dissecans (OCD) is a joint disorder that results in a partial or complete disconnect of articular cartilage from its subchondral bone underneath. The prevalence of OCD is gradually rising in the juvenile population, which may be related to earlier involvement and year-round participation in sports among children. This makes juvenile OCD an increasingly pressing issue since there are many questions that still remain regarding its etiology, diagnosis, and treatment.

OCD of the knee most commonly occurs in the weight bearing femoral condyles. Pediatric patellar and trochlea OCD are uncommon (5-10%) forms of juvenile knee OCD, and there is little information in the literature about how they differ from juvenile OCD of the knee in the femoral condyles. Currently, there are no set guidelines for the treatment of pediatric knee OCD causing physicians differ in their recommendations. If not corrected upon early recognition, pediatric OCD can lead to adult OCD, which can lead to increased pain, reoccurrence of the condition, or premature degenerative joint disease. The goal of this project is to determine the predictors of better outcome and outcomes of surgical treatment of pediatric patients with osteochondritis dissecans of the patella or trochlea of the femur. To our knowledge this will be the largest published case series on surgical management of OCD of the patella and trochlea.

Thirty-three patients (aged 9-18 years) that underwent surgical treatment for patellar and trochlear OCD at Children's Hospital Boston between 2002-2011 and were retrospectively analyzed. Among some of the statistics collected included: gender, age, operative leg, BMI, primary location of lesion, stage of lesion, status of physes, procedure type, and complications including re-operation.

Out of our 33 patients, 22 were male (66.7%) and 11 were female (11%). Due to bilateral surgeries on three patients, there were 36 knees in the study, with 20 left knee operations (55.6%) and 16 right knee operations (44.4%). The most common location of the OCD lesion was on the lateral trochlea, occurring in 41.7% of the knees (n=35). The most frequent stages of lesions encountered by MRI staging was Stage 3 (Hefti scale) with 47.6% (n=21) and by arthroscopic staging was Stage 1 (Gruhl scale) with 38.9% (n=36). The surgical procedures varied between eight different types, with arthroscopy, drilling of the lesions and lateral release as the most frequent choice (100, 83.3, and 66.7% respectively). Re-operation occurred in 5 knees (13.9%).

We are utilizing functional knee surveys (Marx and Tegner Activity Scores, Pedi-IKDC), an independently created Return to Sports Survey, and review of prior clinical notes to determine surgical outcomes and complications. Statistical analysis will then identify which predictors mattered most in the outcome of the patients, and hope to provide insight into which surgical treatment provides the best outcome based on patient characteristics.
CUGBP1 is a splicing factor usually expressed in the fetus, which is thought to be upregulated in Myotonic Dystrophy Type I (DM1). It contributes to the observed pathology by reverting adult transcripts to their fetal isoforms. Recent studies of DM1 mouse models, heart tissue from DM1 patients, and cell lines expressing the toxic CUG repeats, have shown CUGBP1 to exhibit an acidic shift on a 2d gel. This shift has been attributed to phosphorylation of the protein, which is hypothesized to increase the half-life of the protein in the nucleus. Computational predictions have identified several potential phosphorylation sites on the protein between the RNA binding domains, though no antibodies exist against the phospho-protein. This project sought to investigate the PKC family of kinases for their alleged role in CUGBP1 phosphorylation and to implicate a specific PKC isoform as the kinase responsible for CUGBP1 phosphorylation.

Unfortunately, developing an assay to test the effects of PKC knockdown, has proved challenging. This “phospho-shift” does not appear to be present in human cell lines expressing the CUG repeats, though heart tissue taken from human tissue does show it. This assay has not proved robust enough to examine factors which regulate CUGBP1 phosphorylation, so a new assay is being developed. Fibroblasts from human families containing individuals affected and unaffected with DM1 are going to be studied to look at their CUGBP1 phosphorylation status. Splicing events regulated by CUGBP1 are also being examined as a proxy for CUGBP1 activity. Once an assay has been established, the effects of specific PKC isoform knockdown on CUGBP1 phosphorylation and stability will be tested.
Local inflammation imaging to predict atherosclerotic plaque rupture

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The majority of acute coronary events, such as myocardial infarction and sudden death, arise from atherosclerotic lesions with less than 50% stenosis. However, current tools to image atherosclerosis and assess risk focus on anatomical changes, like vessel narrowing. In vivo molecular imaging may provide a method to more accurately characterize plaques and determine risk according to biological processes occurring at a molecular level. In this study, in vivo near infrared fluorescence (NIRF) imaging employing intravascular catheter technology was used to detect local inflammation at high-resolution in an animal model of plaque rupture.

A new macrophage-targeted magnetofluorescent molecular imaging agent, CLIO-CyAm7, was investigated to detect inflammation. CLIO-CyAm7 has not been previously studied in large animals suitable for intravascular imaging. CLIO-CyAm7 is phagocytosed by plaque macrophages, a key driving process in atherogenesis.

A rabbit model of aortic atherothrombosis was employed. The aorta is similar in caliber to a human coronary artery. Atherosclerosis was induced using a 12-week hyperlipidemic diet, with alternating high cholesterol diet (HCD) and normal diet, and aortic balloon injury at 2 weeks. Rabbits were imaged using in vivo NIRF molecular imaging and intravascular ultrasound (IVUS) structural imaging before pharmacological thrombosis triggering. Thrombosis was triggered over 48-hours using Russell’s Viper Venom, a procoagulant and endotoxin, and histamine, a vasoconstrictor. Evans Blue dye was injected prior to sacrifice as a fluorescent marker of endothelial permeability and thrombus. After sacrifice, aortas were imaged using fluorescence reflectance imaging (FRI) and embedded for histological analysis.

Rabbits (n=12) were placed on HCD. Seven rabbits underwent in vivo imaging and pharmacological triggering, with two control rabbits. Three rabbits were sacrificed early due to CLIO-CyAm7 toxicity or HCD related health issues. Atherosclerotic plaque was identified using IVUS. Plaque macrophages were detectable via in vivo 2D NIRF imaging of CLIO-CyAm7 distribution. Ex vivo FRI showed macrophage CLIO-CyAm7 signal distinct from FITC-based autofluorescence and Evans Blue-based endothelial permeability measures. Fluorescence microscopy and H&E staining showed CLIO-CyAm7 localization in macrophages and plaque rupture in two rabbits.

This study showed that inflammatory plaque macrophages in coronary artery-sized vessels can be visualized in vivo via intravascular NIRF molecular imaging. This finding provides a new tool to elucidate the role of macrophages in vulnerable plaque development and rupture. Future in vivo studies will determine whether local macrophage accumulation will predict plaque rupture at inflamed sites. The long-term goal is to harness intravascular NIRF molecular imaging to refine clinical risk prediction of coronary atherosclerosis.
Massachusetts Health Care Reform and the “Young Invincibles”: Analysis of Insurance Coverage for Injured Patients Utilizing the Emergency Department

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The passage of Massachusetts (MA) health care reform law (HCR) in 2006 created a microcosm for study of the impact of “near” universal coverage. Insurance coverage represents potential access to care but is also a proven predictor of care outcomes. Significant strides have been made in broadening coverage, as evidenced by the lowering of the rate of uninsured adults between the ages of 18-65 to 4.8%. However, with injuries historically accounting for approximately 25% of MA Emergency Department (ED) volume, the need remains to evaluate the impact of MA HCR on ED utilization by the largest subset of injury-related trauma patients – the “young invincibles”. These patients are of ages 20-29 and have nationally been the fastest growing segment of uninsured. In a retrospective review of statewide aggregate level ED visit data from Oct 2002 – Sept 2010, the trend of acquisition of insurance coverage in injured patients was established during the implementation of HCR. While both injured patients and those with all other diagnoses had increased rates of public insurance coverage over the time period, the rate per 1000 of uninsured decreased substantially for young invincible injury patients from 2009-2010 of ages 20-24 and 25-29 from 17.5 to 4.1 and 15.2 to 4.1, respectively. A similar trend this steep was not seen in the non-injury population. While further correlation to HCR mandates is needed, this drastic decrease in uninsured young invincible injury patients demonstrates the success of MA HCR in accomplishing a state level solution to an age-specific national problem.
“Building Back Better”: Laying the Foundations for a GHD Case Study on Mirebalais Hospital

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Background: With 80% of the Haiti’s health infrastructure destroyed after the earthquake, the task of rebuilding the already-limited health care system has never been more critical and challenging. The hospital in Mirebalais offers hope. Yet the new hospital is particularly significant to the Haitian people not only as a symbol of the motto “Build back better,” but a replacement of an inadequate public hospital that closed in 2008, leaving 140,000 people without essential medical care. When it opens in early 2012, it will become the largest public hospital outside of the capital city, offering previously unavailable services such as an intensive care unit and an operating theater complex with six operating rooms.

Objective: The goal of this Global Health Delivery (GHD) Project case study is to understand how the construction of a teaching hospital in Mirebalais fits into the health systems strengthening strategy of PIH/ZL and the Government of Haiti.

Methods: Background investigation of primary documents, site visits, and preliminary interviews were conducted to understand the context around the construction of Mirebalais hospital.

Results: An outline was developed for the case as follows:
1) A background section on Haiti’s health system, the effects of the earthquake, and a brief history of PIH/ZL’s work to build health infrastructure in Haiti.
2) A narrative about why, before the earthquake, the town of Mirebalais wants PIH to build a hospital there and how PIH arrived at the decision to do this.
3) A narrative describing why the MSPP/MOH wanted to turn the original plans for a district hospital into a tertiary care, academic medical center. This will include what ZL/PIH thought about this, the tradeoffs and benefits considered, and where they think this new facility fits into the overall health system and national health strategy.
4) Information about the plan to fund the construction and operation of the hospital and the plans to staff the hospital. The case will end as the construction team begins to break ground.

Conclusions: Despite the ubiquitous nature of medical infrastructure, there is a dearth of academic literature that delves into the complexity of scaling individual initiatives as part of health systems strengthening. Developing and disseminating case studies such as this one on Mirebalais may aid this effort in learning how to capitalize on positive synergies between GHIs and health systems.
Impact of a Change in MRI Ordering Policy on the Utilization of MRIs within the BIDPO Care-Network

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Advanced medical imaging modalities represent a significant portion of both total healthcare spending and spending growth in the United States. During the period from 2000 to 2006, Medicare spending on advanced imaging (MRI, CT, PET, and nuclear medicine) has risen $4.0 billion dollars, reaching a 2006 total of $7.6 billion. Averaging a 17% yearly increase, national spending on medical imaging is projected to total $100 billion from 2006 to 2016. These increases in spending have prompted a variety of unsuccessful responses to control the growth in medical imaging costs, ranging from the American College of Radiology’s Appropriateness Criteria to payer adoption of radiology benefits management programs. Not even group-model HMOs have managed to contain these increases. In light of rising spending, managing the cost of advanced medical imaging stands at the center of many policy decisions.

Findings such as these, coupled with this cost-crisis environment, have led to a decision by the Beth Israel Hospital Physician’s Organization to recommend that PCPs no longer order MRIs for patients presenting with knee injury in December of 2010. With the expectation that a specialist may be better trained to appropriately identify whether an MRI is clinically indicated, the hope is that overall utilization of MRI amongst the patients seen by BIDPO will decrease.

After requesting all orthopaedic (shoulder, hip, knee, and ankle) MRIs ordered at the BIDMC six months before and after the BIDPO recommendation, we have been able to provide a department-level breakdown. There has been a statistically significant decrease (p = 0.0469) in the number of orthopaedic MRIs, measured by a paired-two-tailed T-test.

Further investigation would include correction for the number of patient-visits during the two time-periods and elucidation of the greater trends in MRI ordering. There may be other factors leading to this decrease in orthopaedic MRIs aside from the BIDPO recommendation. For example, there is a trend for physicians to request MRIs from other imaging centers. As such, the total MRIs ordered by BIDPO physicians may not be decreasing, rather shifting from BIDMC to other community sites due to cost or insurance factors. As such, it will be necessary to use the BIDPO database to evaluate the role of these trends in the data.
Prevalence of Obesity, Metabolic Syndrome and Associated Risk Factors in Patients Affected by Food Insecurity

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Recent studies with refugee populations have indicated that 85% of households that recently migrated to the US and 33% of those that have lived at least 3 years in the US faced food insecurity. Interestingly, obesity has been associated with food insecurity. Food insecurity has been linked to overweight condition and obesity in adult women; especially those who are mildly food insecure or marginally food secure. According to preliminary data from the Food for Family Program at Chelsea Health Centre, 18% of the families screened randomly in the Adult Medicine department from June 2009 to January 2010 were found to be food insecure. The goal of this project was to determine the prevalence of obesity and metabolic syndrome in a food insecure population at the Massachusetts General Hospital Chelsea Health Center (MGH CHC). Chelsea Health Centre serves one of the highest proportions of immigrants and recent refugees in the state. The prevalence of obesity in the food insecure population was determined to be 49.7%. This prevalence was significantly higher than the prevalence of patients seen at MGH Chelsea Health Centre, which had been estimated to be about 40%. A logistic regression model with obesity as the outcome showed that male gender, being a Spanish speaker, and older age were associated with obesity. However, none of the associations were statistically significant. Based on the diagnostic criteria, the prevalence of metabolic syndrome in the study population was 39.5%. This was higher than the prevalence in the US population identified by National Health and Nutrition Examination Survey (NHANES) 2003-2006 survey, however, the difference was not found to be statistically significant.
Activation of the medial amygdala in socially isolated and group housed mice following social interaction

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Decreased sociability is characteristic of myriad neurological disorders, including autism and schizophrenia. The social withdrawal of these conditions is disabling and treatment refractory, so effective treatment options are urgently needed. However, treating this deficit is complicated by our poor understanding of the neural circuitry underlying sociability. The medial amygdala (MeA) appears to play a vital role in social behavior. This brain structure processes social stimuli from the environment and has downstream projections to the hypothalamus and brainstem to induce behavioral and physiological responses. In addition, the MeA has high densities of oxytocin receptors, which are essential for social recognition and affiliation.

Because of the integral role of the MeA in sociability, we hypothesized that higher levels of sociability would be associated with higher activation of the MeA. To test this hypothesis, we ran mice that were either group housed or socially isolated for 48 hours through a vocalization behavioral assay with a conspecific mouse. Mice that are acutely isolated show increased sociability when exposed to another mouse. The vocalizations emitted by the test mouse during the five minute vocalization assay were quantified as a measure of sociability. Test mice were subsequently sacrificed, and neural activity was assessed by FOS immunocytochemistry. To get baseline neural activity, we performed FOS immunocytochemistry on group housed and socially isolated mice that had not been through the vocalization assay. The number of stained neurons in the medial amygdala was counted.

As expected, socially isolated mice (n=15) showed increased vocalizations compared to group housed mice (n=15); 947.3±376.8 vs 147.2±185.4, t-test, p<0.05. At baseline, the socially isolated (n=2) and group housed (n=2) mice showed similar levels of neural activity in the MeA (118.9±11 stained neurons vs 113.3±23.7, t-test, p>0.05). Additionally, socially isolated (n=1) and group housed (n=8) that are exposed to the vocalization assay appear to show no difference in MeA activity (171 stained neurons vs 173.1±15.3, t-test, p=0.05).

Due to the small sample size, we could not make any definitive conclusion about the neural correlate of increased sociability. However, the data do not suggest that there is differential activity of the MeA between socially isolated and group housed mice during the vocalization assay. Future directions include quantifying neural activity in additional nuclei of the amygdala or other brain regions implicated in sociability.
Execution of an expert panel on malaria rapid diagnostic tests

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In the last decade, millions of malaria rapid diagnostic tests (RDTs) have been implemented worldwide. These simple and easy-to-use tests can diagnose malaria from blood in about 15 minutes making a laboratory diagnosis possible at all levels of the health care system. While the tests have enabled better access to malaria diagnosis, many challenges still remain. For example, test performance is influenced by external factors such as high temperatures, disease prevalence, and user training; physicians do not always believe the test results and prescribe anti-malarial treatment anyway; and maintaining a consistent RDT supply chain is challenging with volatility in funding and procurement processes. In an effort to address these and other challenges with the delivery of RDTs, I created and executed a 3 session expert panel that ran from July 5 until July 20. I invited expert panelists as well as participants from around the world to discuss challenges with the delivery of malaria rapid diagnostic tests in resource-limited settings. Throughout the three weeks, 8 experts participated in the conversation from organizations such as USAID President’s Malaria Initiative, FIND, PATH, University of Lagos, Nigeria, University of Yaoundé I, Cameroon, London School of Hygiene and Tropical Medicine, WHO, and the FDA. Session 1 addressed the RDT test and the challenges with interpreting test results in context. Session 2 highlighted challenges with RDTs and health care provider behavior. Session 3 focused on policy issues including the assessment, procurement, and financing of RDTs. There was a robust discussion with participants from a variety of countries including South Africa, Namibia, and Haiti. A discussion brief was written to summarize the panel discussion; it is available as a resource for all GHDOOnline members.
Hand hygiene has been one of the main focuses of hospital quality improvement; however, to our knowledge the economic costs of hand hygiene policies have never been examined. In this study, we were particularly interested in examining the policy surrounding hand sanitization and glove usage. Many hospitals, such as the Brigham and Women’s Hospital Emergency Department (BWH ED), maintain a policy of hand sanitization before and after each gloving event. Data supporting the practice of hand sanitization before glove-donning is inconclusive. This provides an opportunity for the examination of hospital policy in accordance with both scientific and economic principles.

We therefore designed this study to begin to address the economic effects of hand hygiene policies by assessing the cost in provider time of the glove-donning policy at BWH ED. Time required for hand sanitization and glove-donning event was measured in two ways: first, by following residents in the ED for 2 hour shifts and recording the number of times they donned gloves, controlled for by the number of patients present in the ED, and second, by recording the time to don gloves in a controlled environment with and without the use of alcohol-based hand rub. We hypothesized that the BWH ED policy would cause a significant time burden. In addition, we expected a difference between the actual time burden currently experienced in the BWH ED, and the “maximum burden,” the burden that would be experienced if the Center for Disease Control and Prevention (CDC) standards for hand hygiene were utilized.

We found that alcohol-based hand rub use before gloving is a considerable time burden for ED physicians relative to glove donning. However, glove use overall represents a small proportion of the overall burden of hand hygiene, as the average emergency medicine resident uses gloves less than 1 time per hour, or on approximately one quarter of patient interactions. The average resident physician studied spends 32.5 seconds per event on hand hygiene associated with glove use, of which 53% is spent on pre-glove hand hygiene. Most providers did not wait 30 seconds for alcohol hand rub to dry before putting on gloves; following the recommendation to do so would add additional time to this calculation. Future studies should establish whether or not hand rub provides additional benefits beyond standard exam glove usage for nonsterile procedures in order to understand the full economic and medical implications of current hand hygiene policy.
Barriers, enablers, and preferences of Indigenous Australians in the provision of healthcare and healthcare related services in Geraldton, Western Australia

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The project sought to identify the barriers, enablers, and preferences of Indigenous Australians in the provision of healthcare and healthcare related services in Geraldton, Western Australia, with applications throughout Western Australia. The rationale for the project is that there is a disease incidence and treatment gap between non-Indigenous and Indigenous Australians, and that the process of remedying this gap begins with efforts to discern patient preference and both physical and cultural barriers to care.

Interviews carried out among Indigenous and non-Indigenous social workers, clinical case managers, nurses, rural health nurses, general practitioners, specialist providers, and individuals involved with Indigenous care indicated that Indigenous cardiovascular patients, upon initial presentation for a cardiovascular event, suffer from more advanced cardiovascular disease, at younger ages, than non-Indigenous patients. Reasons given by respondents for earlier presentation of more severe disease in Indigenous patients include: (1) Lack of trust in the Western medical system. (2) Feelings of ‘shame’ and discomfort on the part of Indigenous patients when in a hospital environment. (3) Lack of knowledge about exercise and cardiovascular health. (4) Lack of access to appropriate foods and medications. (5) Difficulty understanding and adhering to medication and rehabilitation regiments.

For the CUCRH project to develop a Palliative Care handbook for healthcare providers working with Indigenous patients, preliminary analyses indicate generally that among both Indigenous and non-Indigenous populations in Western Australia: (1) There is a lack of understanding of the purpose of Palliative Care to enhance quality of life for patients with terminal chronic disease, not only among Indigenous patients, but among Australians generally. (2) Indigenous Palliative Care patients have a variety of views and are grateful if the healthcare professional asks specifically about preferences regarding place of death, funeral arrangements (an issue of particular significance to the Indigenous community), healthcare proxy, and treatment of the body after death. (3) Aboriginal Healthcare Workers (AHWs) and Aboriginal Liaison Officers (ALOs) of both genders facilitate communication, especially in challenging situations. (4) An interdisciplinary approach, utilizing the resources and abilities of social workers, at-home nursing staff, inpatient staff, AHWs and ALOs, and physicians leads to the best outcomes for Indigenous patients.
Identification and Management of Pediatric Malnutrition at a District Hospital in Rwanda

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Malnutrition is a major problem in Rwanda, contributing to approximately half of all morbidity and mortality in children under five. Across the country, 52% of children under five suffer from chronic malnutrition (stunting), 22% are underweight, and 4% suffer from protein energy malnutrition (wasting). Despite Rwanda’s many gains in health indicators over the past decade and a half, rates of malnutrition have remained relatively unchanged.

At the district hospital under review, the Inpatient Malnutrition Unit (IMU) is responsible for managing pediatric cases of acute malnutrition. Although the program has been successful at rehabilitating a number of malnourished children, gaps exist. If the program is to meet the government’s target of a 30% reduction in all forms of malnutrition by 2013, these gaps must be identified and steps taken to redress them.

The objective of the project was to assess whether malnourished children admitted to a district hospital were being identified and treated according to Rwandan national protocol. A review of pediatric admissions between January 1st and June 30th, 2011 was divided into two parts: 1) Pediatric malnutrition admissions (all children 0-17 years admitted to the IMU) and 2) General pediatric admissions (all children 6-59 months admitted to the pediatric ward, excluding children admitted to the IMU). The data collected was for use by the hospital in their efforts to improve the quality of care provided for malnourished children in the district.

The chart review yielded a number of major findings. Of children admitted to the IMU, 64% of children did not receive complete growth measurements as required for their age group. Discharge data indicated that 85% of children admitted to the IMU were released from the hospital without meeting the discharge criteria stipulated in the national malnutrition protocol. Of the children that were discharged, only 41% received a referral for follow-up. Amongst children admitted to the general pediatric ward, it was found that 28% satisfied the diagnostic criteria for acute malnutrition on admission (18% with moderate acute malnutrition and 10% with severe acute malnutrition). Only one of these cases was identified accordingly and referred to the IMU; the remaining 43 children were never diagnosed with malnutrition.

Based on these findings, a series of recommendations was presented to the hospital. The hope is that their implementation will lead to concrete improvements in the identification and management of future cases of pediatric malnutrition at the district hospital level.
Development of an improved volumetric modulated arc therapy (VMAT) treatment planning algorithm

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Volumetric modulated arc therapy (VMAT) is a type of external beam radiation therapy that delivers radiation with a continuously rotating beam of intensity modulated fluence fields. VMAT has a potential to deliver radiation much more efficiently and with better quality than conventional intensity modulated radiation therapy (IMRT). However, widespread VMAT implementation has been hindered by a lack of quality treatment planning algorithms, which are difficult to create due to the non-linear nature of VMAT.

Our objective in VMAT treatment planning is to develop an algorithm to create highly optimal VMAT fluence maps that can be delivered within a clinically acceptable amount of time, as time is proportional to the amount of harmful scattered dose. We first hypothesized that we could create a high quality VMAT plan by approximating the continuous arc with 180 static fluence maps, and then make the plan clinically deliverable by merging neighboring fluence maps to increase the time efficiency without reducing dose quality.

To test this hypothesis, we created a full treatment planning software system in Matlab (Mathworks) called vmerge, which both optimizes initial fluence maps and makes them machine deliverable. We implemented a modified unidirectional dMLC leaf-sequencing algorithm to specify the required linear accelerator machine parameters (leaf speed, gantry speed, dose rate) at each point of the arc. Neighboring fluence maps are merged using a greedy search strategy that iteratively combines the most similar fluence maps and then recomputes the dose. Fluence map similarity is defined as the Frobenius norm of the difference between neighboring fluence maps. Merging is halted immediately before the dose quality begins to degrade, measured as the standard error from the prescription of the dose to the target. We also implemented vmerge in the widely used VMAT software SmartArc (Phillips).

We tested our algorithm on a prostate, pancreas, and brain case. Our planning algorithm met all known dose guidelines with the initial 180 fluence map solution. Initial treatment times before merging were 906s, 859s and 522s for the prostate, pancreas and brain, respectively, and were reduced to 311s, 202s and 228s after merging. Dose quality degradation after merging was less than 1% for all cases. Our initial data from the SmartArc implementation of vmerge indicates that vmerge creates higher quality plans than those generated by the current clinical standard in VMAT planning. We believe that vmerge represents a promising step forward towards creating safer, higher quality VMAT plans.
**Mycoplasma genitalium and preterm delivery at an urban community health center**

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*Mycoplasma genitalium* (*MG*) has been identified in the genital tract of women, but little is known about its pathogenic potential. Although large-scale population-based studies are lacking, prevalence of *MG* in women has been estimated between 4% and 6% in the general population. In one study of high-risk women, the prevalence was 19.2%.

Approximately 12% of births in the U.S. are preterm, and 80% of these are caused by idiopathic preterm labor. Preterm delivery (PTD) is the leading cause of perinatal morbidity and mortality in the industrialized world, with blacks consistently having the highest PTD rates in the United States. Several reproductive tract infections including *Chlamydia trachomatis* (*CT*), *Neisseria gonorrhoea* (*GC*), and *bacterial vaginosis* (*BV*) are associated with preterm labor. Although a relationship between *MG* and PTD is not proven, one study identified an independent association between *MG* and spontaneous PTD. Other work suggested *MG* can ascend and may permanently damage fallopian tubes. In order to better understand the medical significance of *MG* colonization, we sought to estimate its prevalence and investigate its association with PTD. Ultimately, we would like to examine if *MG* infection might explain some of the racial disparities in preterm birth.

Our ongoing pilot study follows 100 women ages 18-45. Subjects were recruited from the Dimock Center in Roxbury, MA, an urban community health center with a higher prevalence of PTD and low birth weight babies than the general population. Our first aim is to calculate the proportion of women who are colonized with *MG* (determined by PCR) at both initial and 34-36 week visits. Additionally, prevalence rates of *CT*, *GC*, *BV* and abnormal pap smear results during pregnancy will be determined.

The second aim is to test if antepartum cervical *MG* colonization is associated with preterm delivery (<37 weeks) or low birth weight (<2500 grams) using log-binomial regression. We will conduct this analysis after all subjects have delivered and control for potentially confounding infections.

Preliminary data analysis provided the following antenatal infection prevalence rates: 8.4% first trimester *MG* (n=95), 9.1% third trimester *MG* (n=33), 5% *CT* (n=100), 1% *GC* (n=100), and 46% *BV* (n=100) infection. Pap smear results were abnormal in 14.3% of women (n=91). To date, 42 women have delivered; 14.3% of infants were preterm and 19.0% were low birth weight. Results suggest that black women have higher rates of prenatal infection and worse birth outcomes than white or Hispanic women, consistent with previous studies.
Cervical Cancer in Peru

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Cervical cancer is the leading cause of death among Peruvian women aged 15-64 years old. Cervical cancer outcomes are significantly better when they are caught in earlier stages of disease where curative solutions still exist. CerviCusco is a Peruvian non-profit established in coordination with the Georgia Health Science University that works to screen as many women as possible with the hope of catching earlier stages of the disease. The “Dia del Mercado Campaign” is an initiative with a correlated study is designed to assess the impact of accessible cervical cancer prevention in a remote Andean indigenous population and its effects on disease detection and subsequent management.

Based on the results of this project, CerviCusco will have a stronger sense of how receptive the community is to its public screening programs. After receiving screening for both cervical and breast cancer (via pap smear and physical exams respectively) in tents or community health centers at these rural market gatherings, as part of the Dia del Mercado Screening Program, women will complete a brief questionnaire gathering demographic data, barriers to treatment and general satisfaction with the screening campaign. The study aims to identify key barriers to screening and follow-up treatment, while simultaneously assessing if women feel urgency or need to undergo Pap smear screening and follow-up treatment (if deemed necessary). This project will be a survey study that will recruit women between the ages of 16-65. The entirety of the study will continue for 24 months, during which more than 5,000 women will hopefully participate. All eligible women will receive an invitational letter describing this brief study of rural Pap smear testing. The results from the study are pending both further data collection and statistical analysis.
Melanocyte and Melanoma Regulation

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Melanoma is a cancer of melanocytes, the cells that produce the dark pigment responsible for skin color. Melanoma is the deadliest form of skin cancer; although melanoma accounts for only 4% of dermatologic cancers, it is responsible for 80% of deaths from skin cancer. While the incidence of melanoma is rising at an alarming rate, long-term effective systemic therapies remain limited.

Pathologic characteristics of melanoma, such as escape from growth inhibition and enhanced metastatic potential, may be linked to its origin as a melanocyte. During development, melanocytes derive from the neural crest, sharing a multipotent progenitor cell with Schwann cells. Melanocyte specification and maintenance require the expression of microphthalmia-associated transcription factor (mitf), which activates the transcription of genes required for melanin synthesis and cell cycle regulation. Not only is MITF critical to regulating melanocyte differentiation and survival, it is proposed to function as a lineage-survival oncogene that promotes melanoma tumorigenicity. Altering the lineage identity of a melanoma by changing its transcriptional environment could disrupt essential signaling pathways specific to melanocytes and favor the adoption of a more benign phenotype. We hypothesize that mechanisms that disfavor the melanocyte lineage (such as forced expression of krox-20, the master regulator of Schwann cell fate) will also inhibit melanoma formation and promote survival.

The vertebrate model organism Danio rerio (zebrafish) was used to assess the ability of forced krox-20 expression to 1) skew away from the melanocyte lineage during development or reprogram fully differentiated melanocytes; and 2) prevent formation or induce regression of melanoma. Results show that inducing krox-20 expression in zebrafish embryos using a heat shock promoter during early stages of melanocyte development results in decreased melanocyte number (30% decrease, p = 0.038), reduced melanocyte migration (55% decrease in fractional lateral dispersion, p <10^{-5}) and altered melanocyte morphology. Forcing krox-20 expression in the melanocytes of a zebrafish melanoma model increases the time required for melanoma tumor formation (27 weeks vs 19 weeks in control, p<010^{-4}). These findings indicate that krox-20 is able to delay melanoma tumor onset and may divert from melanocyte fate during development. Overall, these data support the use of lineage alteration as a potential novel approach to melanoma prevention and treatment.
The Role of Altered Fluid Flow in Stent Thrombogenicity in Sub-optimal Interventional Settings

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Endovascular therapy using stents has revolutionized the treatment of coronary artery disease; each year, over 1 million stents are implanted into patients in the United States alone. However, stenting comes with its own set of problems, one of which is stent thrombosis (ST), the formation of a blood clot around or near the stent. Despite antiplatelet therapy that puts patients at significant risk for bleeding, the annual risk of ST remains around 1%, and increases with suboptimal interventional configurations such as stent malapposition. As ST cases increase with stent usage, it becomes important to understand the mechanistic basis by which ST occurs to prevent adverse events and improve outcomes.

Stent placement requires operator skill and consideration of local vascular geometries and lesion morphology. When inappropriately placed, stent struts will protrude into the lumen or overembed into the vessel wall, potentially altering flow. We hypothesize that stent malapposition is problematic specifically when it leads to flow disturbances, and that these derangements play a governing role in increasing the risk of ST. As a corollary, malapposition without flow disruption should not significantly increase thrombotic risk. We are examining 3D computational models to characterize the nature and extent of flow recirculation in stent malapposition, and correlate this pattern with observed thrombus distribution from \textit{in vitro} models. A 3D computational model of a NIR stent with a flat malapposed region was created using SolidWorks (DassaultSystemes) and Abaqus (SIMULIA), and blood flow through these stent geometries was simulated in STAR-CCM+ (Cd-adapco). To quantify fluid dynamic regimes with disturbed flow behaviors, we used metrics developed in-house such as the integrated reverse axial velocity (IRV) that computes the net effect of reversed flow regimes within the axial direction.

Flow recirculation zones from stent malapposition extended above and beyond the malapposed site, and into the downstream regions. Compared to the fully-apposed case, the IRV exhibited a local maximum of 184% at malappositions of 5% of the radius, a local minimum of 66% at 15%, and an increasing trend for malappositions greater than 15%.

The velocity profile in the malapposed region suggests that some cases of malapposition lead to plug flow, a type of undeveloped flow, which increases recirculation in downstream-apposed regions. Thus, plug flow interactions between neighboring regions within the stent, when they occur, may play a critical role for flow disturbances. Whether these results will correlate with \textit{in vitro} thrombus formation remains to be seen.
Trends of *in situ* melanoma in U.S. men and women

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Melanoma accounts for 4% of skin cancer, but is associated with 79% of skin cancer-related deaths. It is the fastest growing cancer in the US and worldwide. There have been limited studies in literature assessing the epidemiology of *in situ* melanoma in the US. The aim of this study is to describe the trend in diagnosis, body site of occurrence, geographic variation in incidence rate, and pathological sub-types of *in situ* melanoma.

We investigated the trends of *in situ* melanoma in two national prospective cohorts: Nurses’ Health Study I (1976-2004) and Health Professionals Follow-up Study (1986-2004). From 1977 to 2004, the ratio of *in situ* to invasive melanoma increased 15-fold (from 0.09 to 1.32), with the sharpest increase occurring historically after the initiation of public melanoma screening campaigns in the mid-1980s. The incidence rate of non-specific pathological subtype exceeded that of lentigo maligna. *In situ* lesions were equally likely to be found on the head, trunk, upper and lower extremities of women, but favored the head/neck and trunk of men. The body area most susceptible to development of *in situ* melanoma did not change over time. Melanomas (invasive and *in situ*) that developed at a younger age tend to favoring areas of intermittent sun exposure, whereas those that develop in older individuals tend to favor areas of chronic sun exposure.

Together these findings are suggestive that the increase in *in situ* melanoma may be due to a true increase in the development of *in situ* lesions, improved screening techniques over the past 20-years, but are also likely to be in part, due to lower threshold for diagnosing due to medicolegal pressure.
Early Ambient UVR Exposure and the Development of Multiple Non-melanoma Skin Cancers in U.S. Caucasians

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The existence of a critical period in life when the skin is most susceptible to ultraviolet radiation (UVR) has been described. However, the effect of early, ambient UVR exposure on NMSC development later in life has not been well studied. The aim was to determine the effect of early, ambient UVR exposure on NMSC development later in life.

We evaluate this among 80,275 American men and women from the Nurses’ Health Study and Health Professionals Follow-up Study. Exposure was UV index of geographic location at time of birth, age 15, and 30. Outcome was self-reported lifetime number of NMSC(s). During the 1.5 million person-year follow-up, 11,889 (19.4%) of the women and 5,370 (28.1%) of the men developed \( \geq 1 \) NMSC; 21% of combined population was diagnosed with \( \geq 2 \) primary NMSCs. After simultaneously adjusting for age, gender, hair color, number of sunburns, tanning ability, family history of melanoma, and nevus count, the cumulative relative risks (RRs) for \( \geq 1 \) NMSC for those consistently residing in medium and high UV index states were 1.20 (95% CI 1.14-1.27) and 1.42 (95% CI 1.32-1.53) respectively. In the secondary analysis, we found that the incremental risk of developing \( \geq 2 \) NMSC, compared to individuals with one lifetime NMSC, was also significantly elevated; the multivariate cumulative RRs for those who stayed in medium and high UV index states at all three timepoints were 1.09 (95% CI 1.00-1.91) and 1.15 (95% CI 1.02-1.30) respectively.

Our results provide evidence that persistent, ambient UVR exposure early in life is modestly associated with the development of multiple NMSCs later in life.
Associated Comorbidities in Patients with Vitiligo and Alopecia Areata

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Vitiligo is a pigmentary disorder characterized by loss of melanocytes in the affected skin. Alopecia areata (AA) is an autoimmune disease that results in nonscarring hair loss. Although an association between vitiligo and AA has been described, characterization of patients affected by both diseases has been limited.

This study is a multi-center, retrospective review comparing gender, age of onset, race, education level, and associated comorbidities in patients with documented vitiligo and AA. In this population, 2976 patients had the diagnosis of vitiligo and 3376 patients had the diagnosis of AA. Among these, there were 81 patients with both diagnoses; we limited this study individuals with dermatologist-documented diagnoses of vitiligo and AA (n = 45). We found no gender predilection in this population. Vitiligo development preceded AA in 66% of the cases. The average age of diagnosis of either vitiligo or AA was 33 years, with 25% of the individuals diagnosed prior to age 20 years and 64% diagnosed prior to age 40 years. Fifty-three percent of this group was Caucasian, and 38% was Hispanic. Seventy-five percent were current non-smokers and 62% of the population had never smoked. Eighty-two percent of these patients had associated comorbidities with an average age of 43 years at the time of data collection. The most common comorbidity in this population was obesity (40%), followed by thyroid dysfunction (27%) and eczema (24%). The rate of sexual dysfunction, menstrual irregularities, and infertility was 18%. Other autoimmune skin diseases were also common in this population, including psoriasis (9%) and systemic lupus erythematosus (9%). Approximately 9% of the population suffered from depression.

Overall, we observed an ethnic predilection and a high rate of comorbidities in this population. These findings differed from what is commonly observed in either disease alone. The pathophysiology leading to the high rate of comorbidities is unclear, but genetic and psychosocial factors may play a role.
Identification of Novel Antimicrobials that Target Host Pathogen Interaction using the Model Pathogen, \textit{Legionella pneumophila}.

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\textit{Legionella pneumophila} (Lp) is the causative agent of Legionnaire’s disease, a particularly fatal atypical pneumonia. The bacterium is found in aqueous environments and transmitted through aerosols. Lp is phagocytosed by alveolar macrophages but is able to avoid destruction by evading lysosomal fusion. The evasion is orchestrated through the use of its Type IV Secretion System (T4SS), which is specialized bacterial machinery used to translocate protein effectors into the cytoplasm of eukaryotic cells. This allows the bacterium to survive in a replicative vacuole. It has been demonstrated that without a functioning T4SS the bacterium cannot adequately replicate intracellularly, as upon phagocytosis it undergoes phagosome-lysosomal fusion (PLF) and is destroyed. We therefore performed a high-throughput screen to identify inhibitors of the Lp T4SS with the goal of establishing a new type of therapeutic that targets pathogen-host interaction.

Our screen relied upon the observation that T4SS also acts as a sodium channel. Wild-type bacterial growth is inhibited in the presence of sodium, while T4SS mutant growth is not. Therefore, we sought compounds that would alleviate a sodium mediated growth restriction, presumably through disruption of T4SS. We discovered approximately 200 strong hits in a screen of 235,000 small molecules at the NRSB facility. As an initial test, screening hits were then tested to block intracellular growth of Lp.

I then examined promising candidates in two complementary assays of T4SS function. In the first, I examined whether drugs blocked the T4SS-dependent ability of Lp to prevent fusion of lysosomes with the bacterial phagosome. Using immunofluorescent antibodies against lysosomal-associated membrane protein 1 (LAMP1 – a late endosomal, lysosomal marker) and Lp, I used the colocalization of the two signals to determine PLF patterns. In this assay, a high percentage of colocalization demonstrated an inability of the bacteria to evade PLF by use of its T4SS, as is the case with mutant Lp strains. It was found with several different experiments that wild-type Lp infections incubated with an active compound demonstrated a significantly higher percentage of colocalization than wild-type Lp alone and similar colocalization to a T4SS mutant strain, suggesting that at least a subset of our screening hits are acting specifically. I am also investigating the effect of screening hits on T4SS effector translocation into the macrophage cytoplasm. I am using a technique in which eukaryotic cytoplasm is efficiently separated from infecting bacteria, and the amount of translocated effector quantified using a Western blot technique.
Novel data collection tool and feedback mechanism improve clinician compliance with Operating Room to ICU handoffs

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An effective patient handoff minimizes the risk of preventable communication errors and promotes clinician satisfaction. A recently revised handoff process targeting patient transfers between the operating room (OR) and Neuroscience ICU led to statistically significant improvements in clinician compliance with key steps in the handoff process. Building on this preliminary work, we tested a novel data collection tool and feedback mechanism aimed at further improving and sustaining clinician compliance.

We developed a user-friendly data collection tool to assess compliance with previously defined key elements of an ideal OR-to-ICU handoff (e.g., presence of all handoff participants, arrival of Neuroscience ICU receiving team at the bedside within five minutes of patient arrival, and provision of anaesthesia and neurosurgery report). Neuroscience ICU nurses participating in each OR-to-ICU handoff were asked to observe and collect data for two weeks. Data then were compiled and leaders of each discipline involved (nursing, anesthesia, surgery, and critical care) provided feedback to front-line staff. Following this feedback period, data were collected during a second two-week period to determine the effect of the feedback intervention and to further improve compliance moving forward. Compliance data before and after the feedback intervention were analyzed using the two-sided Fisher's exact test.

Twenty observations were recorded in the initial two-week period and 14 observations were recorded in the second two-week period following feedback. Feedback improved compliance with most key elements of the handoff process, particularly presence of the neurosurgeon during the handoff (p=0.01, two-sided Fisher’s exact test). Compliance with several other key elements were similarly improved up to 100%, including neurosurgeons providing a neurosurgery report and Neuroscience ICU nurses arriving at the bedside within five minutes of patient arrival.

OR-to-ICU handoff compliance improved significantly using a novel data collection and reporting tool that informed leadership regarding system performance. Feedback provided by visible and committed leaders from each discipline was critical to improving compliance. We propose future testing of this validated process to increase handoff compliance in other hospital settings.
Promoting Medical Innovation: The Case of Coronary Artery Stents

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The global market for medical devices is over $209 billion and will grow at an annualized rate of 6-9%. However, the process of developing breakthrough medical technologies remains poorly understood. Some studies point to the public sector’s key role in basic science leading to drug development, but most experts believe that medical technology development occurs in the private sector without substantial contribution from academic scientists. We sought to evaluate this hypothesis using the case example of bare metal stents for treatment of coronary artery disease, one of the most transformative medical devices in the past twenty-five years. We undertook a dual methodological approach to address our research question. First, we used a comprehensive database of patents to identify individuals and institutions that have controlled intellectual property related to stent technology early in the development process. Next, we conducted semi-structured interviews with 15-20 of the primary contributors to coronary artery stent development, identified via searches of the medical literature, patents, and discussions with key local experts. We then compared the results from these two approaches. We found first that 245 total patents were filed related to bare metal coronary artery stents in the years from 1984 (the date of the first issued patent) to 1994 (when the first stent was approved by the FDA for widespread use). Each year from 1984 to 1994 showed an increase in the number of patent filings in this field from 1 in 1984 to 97 in 1994. The majority of patents filed were to private companies (45% of the total). Individual inventors, public companies and non-profit institutions represented 18%, 31% and 6% of filings, respectively. For the top 10 most cited patents in the field, 8 of them were filed by private companies while 2 were filed by public companies. However, analyzing our interviews, we found that most of the key intellectual work and proof-of-concept testing leading to the development of coronary artery stents was performed by physicians affiliated with non-profit institutions such as academic medical centers or hospitals. Thus, we conclude that innovation leading to coronary artery stent development first arose from individual physician inventors in academic medical center settings and only later was taken up by medical device industries. This result is not consistent with the record that emerges from a review of the patents and it challenges common perceptions about transformative device innovation.
Targeting STAT3 in Ovarian Cancer

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As an important transcription factor, STAT3 normally modulates cell renewal and proliferation with a rapid and transient downstream effect. However, in tumor cells, inappropriately activated STAT3 alters the gene expression profile and renders tumor cells particularly unresponsive to cell death signals. Because overactive STAT3 pathway in tumor cells has been correlated with resistance to conventional chemotherapies, targeted inhibition of STAT3 constitutes a powerful therapeutic tool to improve the survival rate and prognosis for cancer patients.

In this study, we hoped to examine the effects of several promising STAT3 inhibitors on ovarian cancer cells. We hypothesize that STAT3 inhibitors would downregulate the STAT3 dependent gene expression and reduce the cellular viability of ovarian cancer cells.

Initially, significantly reduced viability was observed when naïve ovarian cancer cells (OVCAR-8) were treated with STAT3 inhibitors. In addition, levels of phosphorylation of STAT3, as well as other signaling molecules (i.e. MAP kinase, Akt, etc.) have pointed to several distinctive mechanisms of action by different STAT3 inhibitors. Surprisingly, results from quantitative RT-PCR analysis have implied an unexpected and reciprocal relationship between STAT3 inhibition and the levels of some of the endogenous STAT3 target genes. STAT3 RNAi experiments further revealed a moderate A20 upregulation and more importantly, a significant IL8 upregulation, which was proposed to play a crucial role in augmented malignancy of certain tumor cells.

To address this intriguing trend, we proposed that other pathways were activated to “balance” the inhibited STAT3 pathway and one of the candidates was NFκB, a potential activator of IL8 and A20 expression. Techniques such as RT-PCR and Dual-Luciferase® Reporter Assay have indicated that the level of IL8 tracked closely with NFκB activity, suggesting a reciprocal relationship between NFκB and STAT3 pathways. Additionally, when NFκB pathway was activated by either overexpression of NFκB subunits (i.e. p65) or cytokine stimulation (i.e. TNFα), the reciprocal downregulation of STAT3 target genes was observed, further supporting this reciprocal association. Finally, treatment with STAT3 inhibitors correlated consistently with IL8 upregulation, which became less significant when NFκB inhibitors (i.e. harmol and celastrol) were included in a combinational drug treatment.

In summary, our experiments offer interesting questions regarding the role of IL8 upregulation and more importantly, the corresponding alteration of NFκB pathway with STAT3 inhibition. We anticipate that the upregulation of IL8 is likely a downstream effect of two major pathways—induction of NFκB and inhibition of STAT3 pathway.
The Lateralization of Trigeminal Pain Processing in the Brain

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The social cost of pain is ubiquitous and staggering, thus further understanding of pain processing in the central nervous system could lead to more effective treatment and rehabilitation of the millions of patients with chronic and acute pain. One often overlooked aspect is the asymmetry of pain, which has potential clinical significance for understanding the underlying neurobiology and co-morbid changes. Experiments in healthy subjects have demonstrated higher thresholds to induced pain on the right side. Chronic pain, particularly in depressed patients, has been shown to be more often on the left side.

This project attempts to find biological support for and insight into lateralization of nociception (the neural encoding of pain) in the trigeminal system through functional magnetic resonance imaging (fMRI). Nine right-handed subjects (6 male: 3 females, mean 27.5 yr, SD 9.1) have completed the study thus far. We applied heat stimuli at one of three different stimulus levels (44°C, 46°C, and 48°C) to the cheeks, innervated by the maxillary branch of the trigeminal nerve. For comparison, the thumbs were also stimulated (48°C) separate from the face. Each heat stimulus was applied to the left, right, or both sides of the body in a randomized fashion. fMRI scans were performed using a 3 Tesla scanner to identify regions activated. After each scan, subjects rated each stimulus’s pain intensity and unpleasantness on a computerized visual analog scale (VAS). The amount of activation on the left and right sides will be compared.

Previous positron emission tomography (PET) and fMRI studies have explored the possibility of right lateralized activation during pain perception. These regions will be evaluated in terms of the lateralization of nociceptive processing within the trigeminal system, in contrast to previous studies that have evaluated the upper limb. Given that pain ascends through different pathways in the case of the face (trigeminothalamic tract) and body (spinothalamic tract), similar activation of the cortex cannot be assumed. Furthermore, unilateral stimulation has yet to be compared with bilateral stimulation to evaluate hemispheric dominance of pain-related activation. Through greater understanding of the role of brain lateralization in pain processing, we hope that better treatments for chronic pain will be formulated. Preliminary data analysis indicates greater overall cortical activation with right-sided stimuli compared to left-sided, particularly in contralateral sensorimotor cortex. Also, the amygdala and insula show greater right hemisphere activation during bilateral stimulation.