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

**Title***

A 5-YEAR ANALYSIS OF THE VIOLENCE RECOVERY PROGRAM AT BRIGHAM AND WOMEN’S HOSPITAL

**Authors***

Elizabeth A Bryant MPH, Manuel Castillo-Angeles, MD, MPH
Deepika Nehra Marta Chadwick Ramsis Ramsis Leo Andrew Benedict Reza Askari, MD Ali Salim, MD

**PI***

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

Objectives: Our hospital established a violence recovery program (VRP) in 2012 to provide in-hospital and community case management for victims of violence. Our aim was to assess the short term performance of VRP and to describe the patients who utilized the offered resources. Methods: This single-center retrospective study includes patients admitted from 2012 to 2016. Data was obtained from VRP’s database and BWH’s Trauma Registry. Participants approached by VRP but refused further interventions were classified as non-users; those with a minimum of 3 encounters were considered high-users. Demographics and injury characteristics were compared between non-users and high-users. Services utilized by high-users were examined. Results: 447 patients were included; 134 (30%) were high-users. High-users compared to non-users were younger (p=0.0005), more likely to be black (p<0.001), more likely to have sustained a gunshot wound (p<0.001) and had longer hospital lengths of stay (p<0.001). High-users most commonly used housing assistance (63%), employment assistance (59%), and safety planning (41%). Conclusion: Over five years, our VRP provided extensive assistance to 30% of eligible patients. We did not identify any modifiable factors differentiating high-users from non-users. Further work is ongoing to identify barriers to utilization of VRP services to improve utilization and evaluate longer-term outcomes.

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

In 2012, Brigham and Women’s Hospital created a program called the Violence Recovery Program (VRP) to assist patients injured by stabbing or guns with challenges they may face after they leave the hospital. An example would be to help feel safe when they go home or find accessible housing. We wanted to see which patients used VRP the most and which services they used. We looked at patients who were seen by VRP between 2012 and 2016. We decided that patients who refused VRP services would be called non-users and patients who saw VRP three or more times would be called high-users. We included 447 patients. Almost one third were high users. The high users were young, more likely to be black, more likely to have been injured by a gun, and stayed in the hospital longer than non-users. High users used housing assistance, employment assistance, and safety planning the most. Our VRP provided extensive assistance to 30% of patients who could have been seen by them. This suggests that patients may have challenges seeing VRP, especially if they are not in the hospital for a long time. Our next steps will be to determine what these challenges are.

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

Understanding which patients are most likely to use VRP and which services are most commonly used by patients is essential to ensuring VRP is meeting patients' needs.

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First Name*  Last Name*  Academic Degrees*
Sally  Tan  MPH

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Dermatology

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sally_tan@hms.harvard.edu  Medical Student / HMS 5th year

Twitter Handle (if applicable)

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

Title*
The Impact of Dermatologist Density on the Volume and Costs of Dermatology Procedures Among Medicare Beneficiaries

Authors*
Sally Tan, Daphne Tsoucas, Arash Mostaghimi

PI*
Arash Mostaghimi

Abstract Body (MUST be limited to 200 words, anything beyond 200 words will be truncated for print)*
Abstract - Background: The persistent shortage of dermatologists impacts access to care and patient outcomes, and maldistribution of physicians exacerbates this issue. The purpose of this study is to characterize the impact of geographic variations in dermatologist density on the provision of dermatology procedures. Methods: Cross-sectional study using 2013 Medicare Provider Utilization and Payment Database, which includes 100% of Part B fee-for-service charges. Results: There were 10,391 practicing dermatologists in the United States, though they were unevenly distributed, with density (per 100,000 persons >65 years) ranging from 5.3 in the lowest quintile to 54.8 in the highest quintile. Overall, dermatologists billed Medicare for 28 million procedures costing $2.21 billion. Mean billed amount per person >65 years was $15.87 in the lowest density versus $92.02 in the highest density quintile. This suggests a demand elasticity of $14.81 increase in spending per Medicare-eligible individual for each interval increase of 10 dermatologists/100,000 persons >65 years (95% CI: 8.28 - 21.34, p-value: 0.005). Conclusions: There is evidence for supply-sensitive variation in the provision of dermatology procedures for the Medicare-eligible population. Further research is needed to determine the impact of such variations on patient outcomes and whether incentives can better align dermatologists with areas of clinical need.

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

Background: There is a shortage of dermatologists, which leads to long wait times and worse patient outcomes. The purpose of this study is to characterize how variations in supply of dermatologists affect utilization of skin care procedures. Methods: Cross-sectional analysis of a Medicare database of outpatient procedural charges. Results: There were 10,391 practicing dermatologists in 2013, though their geographical distribution was uneven. Density of dermatologists (defined per 100,000 persons >65 years living in an area) ranged from 5.3 in the lowest quintile to 54.8 in the highest quintile. These dermatologists billed Medicare for 28 million skin procedures costing $2.21 billion. Average billed amount for dermatology procedures per Medicare-eligible person >65 years ranged from $15.87 in the lowest density quintile to $92.02 in the highest density quintile. For every interval increase of 10 dermatologists per 100,000 persons >65 years, there is a $14.81 increase in Medicare spending on dermatology procedures. Conclusions: There is evidence for supply-driven variation in utilization of dermatology procedures for the Medicare-eligible population; utilization of skin care procedures increases as a function of dermatologist density. Further research is needed to determine how such variations impact patient outcomes and whether incentives can align dermatologists with areas of clinical need.

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

Supply of dermatologists drives variation in utilization of skin care procedures, suggesting that geographical distribution of physicians has a direct impact on patterns of utilization and healthcare spending. It remains to be seen how such unwarranted variations affect patient outcomes.

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- Regenerative Medicine
- Women's Health & Gender Biology

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

Title*
An Electronic Medical Record (EMR)-Based Pattern Mining Approach to Explore Drug Combinations for Pediatric Pneumonia in a Shanghai Hospital, China

Authors*
Chunlei Tang, Yun Xiong, Christopher J. Vitale, Angela Ai, Jiahong Yang, MPH7, Guangjun Yu, MD8,9, Jing Ma, David W. Bates

PI*
David W. Bates

Abstract Body (MUST be limited to 200 words, anything beyond 200 words will be truncated for print)*
We applied three pattern mining algorithms (FP-Growth, PrefixSpan, and USpan) on 680,138 EMRs from 30,512 pediatric inpatient cases (age range 0 to 17 years old) with simple pneumonia diagnosed in a single children’s hospital in China. FP-Growth mines a complete set of frequent drug patterns. PrefixSpan identifies the frequency of drug use over a particular time interval. USpan considers the drug “utility” defined by the dose, frequency, and timing of use. Each of the three algorithms produced top ten patterns from six age groups (0-3 months, 3-6 months, 6-12 months, 1-2 years, 2-5 years, and 5 years and older) forming a total of 180 drug combinations, which covered the top 40 most frequently used drugs (72.0%) in the whole EMRs. These patterns were then reviewed and evaluated by a panel of medical experts (including 3 pharmacists and 2 pediatricians) to summarize five major drug combination patterns and two treatment patterns. Among which, two unexpected patterns deserve further investigation: 1) medications for enteritis or skin diseases following inhalation treatment even without antibiotics; and 2) using third generation antibiotics as the first line treatment was a common practice especially among newborns.

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

Of the 180 drug combinations identified by the three algorithms among the six age groups, the expert panel summarized five drug combination patterns: 1) antiasthmatics, expectorants, and corticosteroids; 2) antibiotics plus (antiasthmatic, expectorant, or corticosteroid); 3) antibiotics plus medications for enteritis or skin diseases; 4) (antiasthmatics, expectorants, or corticosteroids) plus medications for enteritis or skin diseases; and finally 5) third generation antibiotics followed by more commonly used antibiotics. The panel then identified two major treatment patterns: 1) 42.1% of the EMRs used intravenous (IV) therapy with antibiotics, diluents and nutritional supplements; 2) 13.1% of the EMRs used inhaled medication of various combination of antiasthmatics, expectorants and corticosteroids. To our knowledge, this is the first work that using a pattern mining approach to explore medication treatment patterns. We identified three commonly recognized drug treatments (pattern 1, 2, and 3: i.e., medications for enteritis or skin diseases following antibiotic treatments). In addition, we found two unexpected patterns: 1) medications for enteritis or skin diseases following inhalation treatment even without antibiotics (pattern 4); and 2) using third generation antibiotics as the first line treatment was a common practice especially among newborns (pattern 5). The two unexpected patterns deserve further investigation.

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

Pattern mining is an important subfield of data mining which could utilize multiple algorithms to discover interesting, unexpected, and useful patterns of clinical treatments, but it requires a careful assessment and validation.
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- Regenerative Medicine
- Trauma
- Women's Health & Gender Biology
- Other

If you selected 'other' please specify your research area:
Quality Improvement Initiative

Title *
Bench to Bedside: A Nursing Team Reduces Hospital Acquired Pressure Injuries

Authors *
Margaret Higgins, Beth Melanson, Jeanne Praetsch, Natalie Talbot, Sarah Thompson

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

The BWH Thoracic ICU was noted to have a high prevalence rate of Hospital Acquired Pressure Injuries (HAPI). The June 2016 Pressure Injury Prevalence Survey reported 44% of the ICU patients to have PIs. A quality improvement initiative was developed by the Nursing Quality Program Director, two Certified Wound Ostomy Nurses (CWONs), the Thoracic ICU Nurse Director, and the Clinical Nurse Educator. The goals of this initiative were to achieve greater than 80% bedside nurse attendance at the Pressure Injury (PI) Class and to decrease HAPI prevalence rates. Ninety eight percent of Thoracic ICU nurses attended the 4-hour PI class over a seven-month period. Bedside nurses were involved in a bi-weekly unit-based rounding process lead by the CWONs and clinical nurse educator. Rounding process included discussion of the patient’s history, review of risk, plan of care, and participation in a head to toe skin assessment of every ICU patient. In the subsequent three quarterly PI prevalence surveys, only one Pressure Injury was identified following the quality improvement initiative. A combination of vested leadership, increased education, committed bedside nurses and hands-on, “team oriented” patient rounding process changed Thoracic ICU nursing practice, and improved the nurse sensitive quality PI outcomes.

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

Pressure Injuries can result from bedrest and medical equipment. Hospitals try to prevent these from happening to patients. One intensive care unit at Brigham and Women’s Hospital had high rates of these pressure injuries. To decrease these rates, a team of nurses started a program which included classroom education and every other week bedside rounds lead by nursing experts. Education continued during the rounding process. This unit decreased their rates to only one pressure injury in a nine-month period. Education and the patient rounding process were effective in decreasing pressure injuries.

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

Classroom education in combination with clinical bedside learning, lead by qualified experts, can be an effective combination for improving nurse-sensitive quality metrics.

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- Trauma
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- Other

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

Title*
Cortical Plasticity of Language function in patients with primary brain tumors

Authors*
Prashin Unadkat, Antonio Meola, Laura Rigolo, Geoffrey Young, Raymond Huang, Walid Ibn. Essayed, Alexandra Golby, Yanmei Tie

PI*
Alexandra Golby

Abstract Body (MUST be limited to 200 words, anything beyond 200 words will be truncated for print)*
Introduction: Brain tumors located near eloquent cortex may not be amenable to complete resection due to the risk of post-operative deficits. Long-term brain plasticity especially the ones related to language function may provide a theoretical basis for multi-staged tumor resection that may give time for the brain to reorganize function. Therefore, understanding the potential and dynamics of brain plasticity is vital in surgical decision-making. Methods: We retrospectively evaluated primary brain tumor patients who underwent 2 preoperative fMRI sessions for language mapping at Brigham and Women’s Hospital from 2003 to 2016. A total of 11 patients were included, with mean interval between 2 fMRI sessions being 39.86 months. Three raters assessed the language maps across the two time points, answering questions pertaining to the location of language area activations. Laterality Index (LI) was calculated to assess the changes in language lateralization. Results: Six patients were rated as having new language activations either in the same or contralateral hemisphere as the tumor, and 2 patients having new activations in both hemispheres. The mean change in LI was 0.66+/−0.39. Conclusions: Results indicated the potential for language reorganization in brain tumor patients and may warrant a multi-staged resection to avoid post-operative language deficits.

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

When brain tumors are located near structures responsible for vital functions such as language, motor skills, etc. it may not be possible to completely remove the tumor due to risk of deficit. Studies have suggested the ability of the brain to reorganize itself and understanding it’s potential could allow surgeons to remove the tumor in a step wise fashion thereby giving the brain the time to reorganize function located close to the tumor. We reviewed 11 patients with brain tumors who also had at least two functional MRI (fMRI) sessions to map language function at the Brigham and Women’s Hospital between 2003 and 2016. Three raters assessed the fMRI scans from the two time points. We also calculated the laterality Index to assess the contribution of both the hemispheres towards language function. Six patients were reported as having new activations related to language in the same or the opposite hemisphere as the tumor, and 2 patients had new activations within both hemispheres. The results suggested the potential for reorganization of brain area’s involved with language function, and could warrant a step-wise resection to avoid language deficit.

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

Brain tumor patients may present language reorganization thus opening the possibility of planning a multi-staged tumor resection whenever possible to avoid post-operative language deficits.

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- Women's Health & Gender Biology

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

Title*
The Sleep Matters Initiative: A program to improve sleep health among BWH employees

Authors*
Matthew Weaver, Laura Barger, Stuart Quan, Conor O'Brien, Salim Qadri, Natalie Viyaran, Charles Czeisler

PI*
Charles Czeisler
Sleep disorders are very common. Employees with sleep disorders seldom report these symptoms to their doctors, and when sleep disorders are suspected, multiple barriers impede timely evaluation and treatment by sleep specialists. To overcome these barriers, we sought to implement a comprehensive education, screening and treatment program for common sleep disorders among BWH employees. We enrolled 116 employees in this quality improvement initiative. Employees attended a 90 minute educational session. They were provided with iPads on which they completed knowledge assessments and screening for common sleep disorders. Upon completing the questionnaire, the sleep disorder screening results were presented instantaneously. Those who screened positive were presented with a calendar on which they could select from available sleep clinic appointments. Sleep disorders were highly prevalent, with 37% screening positive for insomnia and 31% screening positive for obstructive sleep apnea. Of the participants who screened positive for a sleep disorder, 58% immediately scheduled an evaluation at one of four special clinics dedicated to this project in the following two weeks. Respondents answered 48% of questions correctly on the pre-test and 69% correctly on the post-test (p<0.01). Overall, 97% of participants considered the information helpful and 98% would recommend the program to others.

Lay Summary: Sleep disorders are very common. Employees with sleep disorders seldom report these symptoms to their doctors, and when sleep disorders are suspected, multiple barriers impede timely evaluation and treatment by sleep specialists. To overcome these barriers, we sought to implement a comprehensive education, screening and treatment program for common sleep disorders among BWH employees. Employees attended a 90 minute educational session. They were provided with iPads on which they completed knowledge assessments and screening for common sleep disorders. Upon completing the questionnaire, the sleep disorder screening results were presented instantaneously. Those who screened positive were presented with a calendar on which they could select from available sleep clinic appointments. Sleep disorders were highly prevalent, with 37% screening positive for insomnia and 31% screening positive for obstructive sleep apnea. Of the participants who screened positive for a sleep disorder, 58% immediately scheduled an evaluation at one of four special clinics dedicated to this project in the following two weeks. Respondents answered 48% of questions correctly on the pre-test and 69% correctly on the post-test (p<0.01). Overall, 97% of participants considered the information helpful and 98% would recommend the program to others.

Clinical Implications: Undiagnosed and untreated sleep disorders are common in our workforce. Providers should consider eliciting information on sleep as part of their clinical assessment. Sleep disorders remain under-recognized and an effort to improve their identification and treatment is needed.

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If you selected 'other' please specify your research area:
Chronic pain treatment

Title*
Case Study: Pain Neuroscience Education Improves Function and Decreases Disability in Patient with Chronic Pain

Authors*
Rachel C. Wilson, PT, DPT

PT*
Rachel C. Wilson
This case study demonstrates the use of pain neuroscience education (PNE) as an adjunct to traditional physical therapy intervention for a patient with an 18-year history of chronic pain. The patient, a 50-year-old male with chronic back pain and neck pain, was referred to outpatient physical therapy for “reconditioning” 4 months after a lumbar fusion surgery. Due to the complex nature of his chronic pain and medical history, PNE was incorporated into his treatment and initiated at his first visit. The PNE included education on pain as a protective mechanism, neuroplasticity, the central nervous system’s primary role in the production of pain and the use of physical activity to alter the aberrant activity in the nervous system, in addition to traditional cardiovascular and strength training to improve physical function. Over the course of treatment, the patient demonstrated improvements in disability and functional mobility and decreased pain catastrophization. The Oswestry Low Back Disability Questionnaire score improved from 75% to 40% and the Pain Catastrophizing Scale score improved from 33/52 to 25/52. This case study demonstrates the role that PNE can play in the management of patients with chronic pain in the outpatient physical therapy setting.

This case study demonstrates the use of pain neuroscience education (PNE) as part of a physical therapy intervention plan for a patient with 18-year history of chronic pain. The patient was a 50-year-old male with chronic back pain and neck pain, referred to physical therapy for “reconditioning” 4 months after a low back surgery. Because the patient had a complex medical and chronic pain history, PNE was included as part of his treatment plan. PNE teaches patients about the biological, protective function of pain as well as how chronic pain can affect the nervous system and change the way that pain is processed in the body and the brain. The patient received PNE along with traditional physical therapy interventions to improve physical function. At the end of the physical therapy sessions, the patient demonstrated improvements in functional mobility, a decrease in pain severity and an increase in participation in his daily life activities.

Physical therapy treatment that includes pain neuroscience education, teaching patients about the protective function of pain and how pain systems function and can be altered, can be effective in treating patients with chronic pain conditions.
First Name*  Jana

Last Name*  Wood

Academic Degrees*  MPharm

BWH Department*  Radiation Oncology

BWH Division (if applicable)

BWH ID Number

Email Address*  jana_wood@dfci.harvard.edu

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- Regenerative Medicine
- Women's Health & Gender Biology

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

Title*
A Justicia plant may hold the key for treating blood-loss related disorders

Authors*  Jana Wood, Sayeda Yasmin-Karim, Michele Moreau, Rajiv Kumar, Wilfred Ngwa

PI*  Wilfred Ngwa

Abstract Body (MUST be limited to 200 words, anything beyond 200 words will be truncated for print)*
Among all the expressed proteins in the human body, hemoglobin has the important role of transporting vital gases. A similar mechanism is also observed in plants. However, the concentration of hemoglobin expressed in plant tissues is orders of magnitude lower (e.g. 0.03 g/dl) than that in human blood; for reference 12.3-15.3 g/dl in women and 14.0-17.5 g/dl in men. We analyzed the leaves of the Justicia plant and discovered an uncommonly high concentration of hemoglobin (over 12 g/dl) in addition to some of the other essential mineral elements in human blood. Equal lyophilized masses of leaf extract and commercial human hemoglobin show comparable hemoglobin levels. Western blot analysis revealed the presence of human α-hemoglobin and the weaker presence of β-hemoglobin. The UV-VIS absorption spectra of the plant extract confirmed the presence of hemoglobin with an absorption peak around 578 nm. Repeated in vitro studies on normal cell lines and mice also proved the non-toxic effects of the extract on the cells and kidneys. The high hemoglobin concentration suggests the potential for utilization in the medical, pharmacological, and food industries.

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

Plants, like humans, contain hemoglobin. It serves as a transporter for oxygen carried into the tissues and transfers carbon dioxide back to the lungs for elimination. In plants, hemoglobin fills the function of nitrogen-fixing symbiosis as a way of producing missing nutrients. Hemoglobin can also facilitate oxygen diffusion or serve as an oxygen sensor. In contrast to humans, plants have a lower concentration of hemoglobin with different structural modifications. However, we have analyzed an extract derived from a plant in the genus Justicia, which has an uncommonly high concentration of hemoglobin. Additional Western blot proteins test revealed the presence of human α-hemoglobin and the weaker presence of β-hemoglobin. For reference, human hemoglobin consists of two alfa and two beta protein units. In addition, the extract contains many of the essential elements found in human blood. These findings directed us to begin research on normal human cells and mice. We did not observe any harmful effects in the test groups. With these positive results, we anticipate that the plant has the potential for pharmacological applications after further research. It could potentially help treat patients suffering from anemia, blood loss, leukemia, or other radiation-related side effects.

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

This research can potentially help treat patients suffering from anemia, blood loss, leukemia, or other radiation-related side effects. It can also be utilized as short term blood substitute.

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Title*

PET Imaging of Pulmonary Arterial Hypertension using Increased Expression of Angiogenic Marker VEGF

Authors*

Peiran Yang, Teresa Dinter, Ivana Nikolic, Lai-Ming Yung, Marie Foley Kijewski, Mi-Ae Park, Shuyan Wang, Peter Holton, Justin Paolino, Anthony Belanger, Shipra Dubey, Aaron Waxman, Marcelo DiCarli, Paul Yu

PI*

Dr Paul B Yu

Abstract Body (MUST be limited to 200 words, anything beyond 200 words will be truncated for print)*
Background: Pulmonary arterial hypertension (PAH) is marked by remodeling of the pulmonary vasculature thought to be related to dysregulated angiogenesis. The angiogenic factor vascular endothelial growth factor (VEGF) are elevated in PAH. We aimed to test radiolabeled anti-VEGF antibodies as positron emission tomography (PET) probes for non-invasive and early detection of PAH. Methods and Results: Immunohistochemistry with bevacizumab (Avastin), a monoclonal antibody against human VEGF1 already FDA-approved as a cancer therapeutic, revealed increased VEGF staining in the PAH lung tissues. Experimental PAH was induced in rats with three week SUGEN5416-hypoxia (SU-Hx) exposure followed by three weeks of normoxia. PET scans of rats were performed 4 days after a tail vein injection with 0.2mCi of activity in 200μg of 89Zr-bevacizumab. PET scans of SU-Hx rats demonstrated increased activity in 89Zr-bevacizumab signal in the peripheral lung fields compared to the control rats. Autoradiography and fluorescence immunohistochemistry confirmed increased 89Zr-bevacizumab signal in the lungs of SU-Hx rats. Conclusion: 89Zr-bevacizumab can be used as a molecular PET imaging probe for VEGF in experimental PAH. Efforts are underway to test 89Zr-bevacizumab PET imaging in PAH patients and to test more sensitive VEGF antibodies in pre-clinical studies.

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Background: Pulmonary arterial hypertension (PAH) is a severe disease where blood vessels in the lungs are blocked, causing increased resistance and blood pressure. Blood vessels grow abnormally in PAH and a protein named vascular endothelial growth factor (VEGF) is increased. Our goal was to use a tagged antibody against VEGF for non-invasive and early detection of PAH. Methods and Results: We used bevacizumab, an antibody against human VEGF1 and a cancer drug (Avastin), to confirm increased VEGF levels in the PAH lung tissues. Radioactively tagged bevacizumab was given to a rat model of PAH and positron emission tomography (PET) scans were performed 4 days later. Scans of PAH rats showed more tagged bevacizumab in the periphery of lungs compared to the control rats. We also confirmed increased amounts of tagged-bevacizumab in the lung sections of PAH rats. Conclusion: Radioactively tagged bevacizumab can be used as a molecular tracer in PAH animal model. Efforts are underway to test this in PAH patients and to test more sensitive antibodies in pre-clinical studies.

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

Increased levels of VEGF may be utilized as a marker of PAH. Radiolabeled-bevacizumab enables early and non-invasive detection of the disease. This method could complement the gold-standard diagnosis by catheterization and allow for an early stage treatment.

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Title*  
Radiation induced cytotoxicity towards circulating tumor cells preventing distant metastasis in pancreatic cancer

Authors*  
Sayeda Yasmin-Karim, Michele Moreau, Stephanie Dougan, and Wilfred Ngwa

PI*  
Wilfred Ngwa

Abstract Body (MUST be limited to 200 words, anything beyond 200 words will be truncated for print)*
Despite of all the improvements of cancer related therapy, the overall median survival period of pancreatic cancer is very short. The most common cause of death is metastasis to distant vital organs. Radiotherapy, a major modality for cancer treatment, can induce tumor regression in non-treated distant sites through an abscopal effect by activating the immune system. An optimum dose of radiation is required to achieve the most desired outcome in this regard. Here we enhanced the abscopal effect of 5 Gy of radiation with an immunoadjuvant (anti-CD40), in a syngeneic murine model of pancreatic adenocarcinoma. With the use of a Small Animal Radiation and Research platform (SARRP) for image-guided radiation therapy, we treat only one tumor among two subcutaneously implanted pancreatic tumors in two flanks. We observed 75% (p>0.001) regression of the volume of treated tumors and 86% (p>0.001) of untreated ones with this single dose of 5 Gy radiation followed by an intratumor injection of anti-CD40. Surprisingly, this combination treatment shows 90% (p>0.001) reduction of distant metastasis formation in lungs. These results suggest that in-situ administration of anti-CD40 antibody following an optimum radiation dose could significantly enhance the abscopal effect to induce the cytotoxic effect in circulatory tumor cell.

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

Despite of all the improvements of cancer related therapy, the overall median survival period of pancreatic cancer is very short. The most common cause of death is metastasis to distant vital organs. It has been observed that radiation treatment at one tumor may lead to reduction of tumor volume in metastatic cancer at other sites, which were not irradiated; this phenomenon is called ‘abscopal’ effect. Unfortunately, this is very rare phenomenon. Here we used an immunologic adjuvant (anti-CD40) to enhance the abscopal effect with only 5 Gy of radiation dose in a pancreatic cancer mouse model. We precisely irradiate only one tumor among two subcutaneously implanted pancreatic tumors in two flanks. We observed 75% reduction of tumor volume of treated tumors and 86% reduction of untreated tumors with this single dose of 5 Gy radiation followed by an intratumor injection of anti-CD40 only in one tumor site. Furthermore, this combination treatment also shows 90% reduction of metastasis formation in lungs. These results suggest that in-situ administration of anti-CD40 antibody following an optimum radiation dose could significantly enhance the killing effect of tumor cells in the circulation to reduce metastatic tumor formation in pancreatic cancer.

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

This treatment methods promotes the idea of treating only one tumor site to get cure of the tumors of all locations and prevent metastasis formation. This advocate the idea of next generation pancreatic cancer treatment model, subcutaneously modulated cancer therapy.

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Title*
Persistent proximal tubular epithelial expression of Kim-1 causes progressive kidney injury in mice

Authors* wenqing yin

PI* Joseph V Bonventre

Abstract Body (MUST be limited to 200 words, anything beyond 200 words will be truncated for print)*
Acute kidney injury predisposes to the progression of chronic kidney disease and the development of end stage renal failure. Previously, we had reported that early and persistent epithelial expression in nephrons of kidney injury molecule-1 (KIM1) causes murine kidney fibrosis and zebrafish tubule damage. Since prenatal activation also decreases nephron number we tested the hypothesis that postnatal activation of KIM-1 expression specifically in renal proximal tubular epithelial cells would lead to fibrosis independent of any potential effect on kidney development. We created proximal tubular cell specific KIM-1 transgenic mice by treating the Slc34a1 Cre-ERT2 mouse with tamoxifen to express KIM-1 in proximal tubules in a postnatal context. The resulting KIM-1PTCtg transgenics were subjected to bilateral renal ischemia-reperfusion injury for 26 minutes. KIM-1 was expressed on the proximal tubular cells after tamoxifen-induced Cre-ERT2 recombination starting at 4 weeks of age. Without any further intervention KIM-1PTCtg mice developed fibrosis with progressive renal insufficiency at 6 months of age, while the kidney function and histology were close to normal at 3 months of age. Bilateral renal ischemia reperfusion injury in KIM-1PTCtg kidneys at 3 months of age cause impaired repair with remained renal insufficiency, leading to progressive kidney fibrosis and renal failure.

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Chronic activation of KIM-1 expression promotes kidney fibrosis and accelerates the progression of chronic kidney disease after acute kidney injury. Persistent expression of KIM-1 may play an important role on the link between acute kidney injury and progressive chronic kidney disease.

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

As well as sensitive biomarker of acute kidney injury, Kim-1 could be potential therapeutic target for preventing progression of chronic kidney disease.

*  

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Title*
Dietary intake of folate, methionine, and vitamin B6 in relation to ovarian cancer survival in the New England Case-Control Study

Authors*
Jennifer J. Yland, Holly R. Harris, Allison F. Vitonis, Daniel W. Cramer, Kathryn L. Terry

PI*
Kathryn L. Terry, Sc.D.

Abstract Body (MUST be limited to 200 words, anything beyond 200 words will be truncated for print)*
Folate, methionine, and vitamin B6 are components of the one-carbon metabolism pathway and are involved in DNA repair. Previously, we found an inverse
association between methionine and vitamin B6 and ovarian cancer risk. However, the association with ovarian cancer progression is unknown. We evaluated intake of folate, methionine, and vitamin B6 among 1,520 women with invasive ovarian cancer in the New England Case-Control (NECC) Study. At study enrollment, participants completed a food frequency questionnaire, covariate data were ascertained through in-person interviews, and blood samples were collected. DNA was extracted from blood samples evaluated for the presence of genetic variants across the genome, including two functional polymorphisms in the MTHFR gene. We used Cox proportional hazards models to estimate the hazard ratios quartiles of nutrient intakes and ovarian cancer survival. Effect modification by alcohol intake and MTHFR polymorphisms was also explored by comparing stratum-specific estimates. The average nutrient levels of dietary folate, dietary vitamin B6, and methionine were 351 mcg/day, 1.8 mg/day, and 1.7 g/day, respectively. Overall, we observed no significant associations between nutrients in the one-carbon metabolism pathway and ovarian cancer survival. Our results suggest that the one-carbon metabolism pathway does not play an important role in ovarian cancer progression.

Lay Summary (MUST be limited to 200 words, anything beyond 200 words will be truncated for print). Please keep in mind - Discover Brigham is open to the public, this lay summary needs to be appropriate for lay audiences with NO scientific background. Folate, methionine, and vitamin B6 are nutrients that are involved in building, repairing, and altering our DNA. They are critical components of 'one-carbon metabolism,’ and their consumption through diet and supplements has been shown to impact biological processes including aging, cardiovascular disease, and cancer. We previously found that differences in methionine and vitamin B6 influenced ovarian cancer risk. Here, we were interested in the relationship between these nutrients and survival, among women with invasive ovarian cancer in the New England Case-Control Study. We collected data on nutrient intake with a food frequency questionnaire, a survey by which participants can indicate how often they have consumed certain foods and beverages. We collected information on other factors, such as oral contraceptive use and family history of ovarian cancer, via in-person interviews. Lastly, we analyzed participants’ DNA for genetic differences. We conducted a variety of analyses to study the relationship between nutrient levels, broken down by quartile, and length of survival among ovarian cancer patients. However, we found no significant associations. This suggests that these nutrients may impact risk and survival differently.

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

Investigation of the modifiable risk factors of ovarian cancer may contribute to advances in treatment as well as prevention. Diet, particularly nutrients involved in one-carbon metabolism, may differentially impact risk and survival. These relationships should be further explored.

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Medical Education

Title*
Outcomes of funded dermatology summer research opportunities for medical students

Authors*
Grace J. Young, Olatunde Badejo, Nicolas Kahl, Bryan Iorgulescu

PI*
Bryan Iorgulescu

Abstract Body (MUST be limited to 200 words, anything beyond 200 words will be truncated for print)*
To encourage medical student interest in dermatology research, many dermatology foundations have supported summer-long and yearlong research fellowships. However, the effects of funded dermatology research opportunities early in a medical student's career have yet to be methodically studied. Systemic analysis of medical student research fellowship programs found 155 programs, 2% of which were dermatology-specific, including the Melanoma Research Foundation, the American Skin Association, and the Lupus Foundation of America. As of 2001, 109 medical student awardees have been financed by these programs. Students received a median stipend of $5,300 over 8-12 weeks of research. Projects were categorized as 75% basic/bench, 15% clinical, 6% translational, 1% socioeconomic, and 3% N/A. 70% of awardees entered the match, 59% of which matched into dermatology, compared to 2.6% of all medical students in the national residency match program. Each awardee has published a median of 5.6 peer-reviewed articles (range: 0-44), at a median of 1.3 articles/post-fellowship-year (range: 0-8.7). Four of the currently practicing awardees have NIH funding, averaging $114,907. Medical undergraduates who engage in funded dermatology or dermatology-mentored fellowships are more likely to publish and match into dermatology. Early funding for this type of research may provide substantial returns-on-investment for future dermatological research and practice.

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

To promote greater interest in dermatology and dermatology-related research, a number of foundations offer summer-long and yearlong funded research opportunities for medical undergraduates. To assess the returns-on-investment of these fellowships, we conducted a review to assess the impact of these funded elective dermatology research opportunities on subsequent career direction. Our analysis suggests that undertaking funded dermatology research opportunities during medical school is associated with higher rates of matching into a dermatology residency, publication of dermatology research, and NIH funding, possibly by allowing recipients to both immerse themselves in and assist in advancing the specialty.

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

Shrinking research funding, combined with increased clinical pressures and patient loads, have contributed to a shortage of physician-scientists in dermatology. A systematic analysis suggests that engagement of medical students in funded dermatology fellowships may provide sizeable returns-on-investment for future dermatological research and practice.

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ML290, an allosteric agonist of RXFP1, attenuates experimental pulmonary hypertension

Authors
Lai-Ming Yung, Ph.D.1; Christopher van Deusen, Ph.D.2; Geoffrey Bocobo, B.S.1; Teresa Dinter, B.S.1; Peiran Yang, Ph.D.1; Marc Ferrer, Ph.D.3; Ken Wilson, Ph.D3; Juan Jose Marugan, Ph.D.3; Alexander I. Agoulnik, Ph.D.4; Paul B. Yu, M.D., Ph.D1.
Relaxin promotes vasodilatation and prevents fibrosis. Role of relaxin signaling axis in pulmonary vascular disease is not established. Pre-clinical and clinical development of relaxin is limited by its short half-life, requirement for continuous parenteral administration, and immunogenicity leading to inactivation. To address these limitations, we tested whether or not ML290, a small molecule allosteric modulator for relaxin receptor (RXFP1), can modulate vascular remodeling and pulmonary hypertension in an animal model. ML290 interacts with human and non-human primate RXFP1, but not rodent RXFP1. Humanized RXFP1 knock-in mice but not wild-type mice are sensitive to the acute hemodynamic effects of ML290. Immunohistochemistry revealed RXFP1 expression in vascular media but not intima of normal human pulmonary arteries, and abundant expression in the hypertrophied media of pulmonary arteries from PAH patients. Relaxin induced ERK1/2 phosphorylation, inhibited TGFβ signaling and regulated phenotypic switch in vitro. Relaxin did not attenuate PH in monocrotaline-treated rats, but was associated with the development of neutralizing antibodies within 7-10 days. ML290 attenuated PH in SU5416-hypoxia treated humanized RXFP1-mice in a dose-dependent manner. Small molecule RXFP1 modulator ML290 ameliorates PH and RVH in RXFP1 knock-in mice, suggesting relaxin/RXFP1 signaling contributes to pulmonary vascular homeostasis and may be therapeutic target in PAH.

Lay Summary
Relaxin is a hormone produced by the ovary and the placenta that promotes tissue remodeling, heart compliance, renal flow and modulates blood pressure during pregnancy. Several animal and clinical studies have shown the capacity of recombinant relaxin hormone to ameliorate pathologic conditions entailing fibrotic conditions, including pulmonary hypertension and pulmonary fibrosis. Despite encouraging findings in cell-based assays and preclinical studies, the clinical development of recombinant relaxin is limited by pharmacokinetics and immunogenicity. The present study examines the therapeutic potential of a novel small molecule agonist in animal models of pulmonary hypertension. ML290 is a compound that activate human relaxin receptor, but not rodent receptors. Mice were engineered to express the human relaxin receptor and were used for present study. We found that recombinant protein failed to modulate pulmonary hypertension in monocrotaline-treated rats, and indeed, relaxin administration was associated with development of neutralizing antibody. In contrast, ML290 dose-dependently prevented pulmonary hypertension and right ventricular hypertrophy in the mouse model of pulmonary hypertension. Our finding shows that relaxin signaling axis is important in pulmonary hemostasis, and represents a novel therapeutic target for pulmonary hypertension.

Clinical Implications
Clinical development of Relaxin is limited by its short half-life, requirement for continuous administration and immunogenicity. ML290, a novel small molecule agonist for relaxin receptor, prevents pulmonary hypertension and represents a novel therapeutic target in pulmonary hypertension and fibrotic diseases.
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Title*
Targeting Transcriptional Addiction for the Treatment of TSC

Authors*
Mahsa Zarei, Heng Du, Rachel E Yan, Yubao Wang, Tinghu Zhang, John M Asara, and David J Kwiatkowski

PI*
David J Kwiatkowski

Abstract Body (MUST be limited to 200 words, anything beyond 200 words will be truncated for print)*
TSC is a multi-system disease marked by loss of TSC1/2, leading to mTOR-hyperactivation and downstream effects on transcription. While treatment with Rapalogs suppresses tumor growth during treatment, regrowth occurs after discontinuation. Recent screens have identified THZ1, a CDK7 inhibitor and selective transcription-targeting drug, as a cytocidal compound for several cancers. We hypothesized that THZ1 is selectively lethal to TSC-null tumors. THZ1 was selectively lethal for the TSC1-null HCV29 bladder cancer and TSC2-null 621-101 angiomyolipoma cell lines compared to addback cells, for which the IC50’s were 6-8-fold higher. FACS assay of apoptosis showed that 37% of THZ1 (30nM, 72 hrs)-treated null cells were Annexin V+ in comparison to 3% of addback cells. RNA-seq and GSEA pathway analyses on samples treated with THZ1 identified genes important to metabolism as significantly altered in THZ1-treated null cells, particularly those involved in glutathione biosynthesis. Metabolite analyses confirmed that THZ1 caused a 4-fold decrease in total glutathione. In vivo, THZ1 +/- Rapamycin eliminated tumor growth in HCV29 xenografts without recurrence of tumor nodules after treatment discontinuation. These findings reveal that THZ1 selectively kills TSC-null cells. Targeting transcription with CDK7 inhibitors developed for human use, such as SY-1365, will likely have major therapeutic benefit for patients with TSC.

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

Tuberous sclerosis (TSC) is a genetic disease in which tumors can develop in multiple organs. TSC is caused by a mutation in the TSC1/2 gene, leading to activation of mTOR. Treatment with mTOR inhibitors shrink tumors in TSC, but when treatment is discontinued, tumors regrow. Hence, continual therapy is needed. Therapies for TSC that induce a complete regression of the tumor without regrowth once the treatment is stopped are not currently available, but would have great benefit for TSC patients. Here, we hypothesize that treatments targeting RNA transcription will eliminate tumor cells with mTOR hyperactivation and achieve a "cure" for tumors in TSC. Our data, from human cell lines that lack the TSC proteins, showed that inhibiting transcription with a novel drug THZ1, triggers a strong and selective death of cells with TSC gene mutations and hyperactive mTOR. We investigated the mode of action of this drug by using RNA-sequencing and metabolomic profiling in cells and mouse models of TSC. With early clinical trials of THZ1 derivatives (SY-1365) in humans beginning by Syros Pharmaceuticals, this treatment has the potential to benefit TSC patients soon. Ultimately, we hope to develop new treatment strategies for TSC that will not require lifelong therapy.

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

Targeting transcription with THZ1 are expected to have significant clinical impact because these treatments may eliminate tumor recurrence following treatment cessation. THZ1 derivatives (SY-1365) for use in patients are being pursued by Syros Pharmaceuticals and are in early clinical trials.

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Title* 
A Novel Automated technique to Improve MR-guided Prostate Biopsy

Authors* 

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

Purpose: Evaluation of a novel automatic 3D Slicer extension for prostate gland delineation based on convolutional neural networks, and a method to rapidly segment the biopsy needle trajectory from MR for better visualization by the interventional radiologist. Methods: Diagnostic axial T2-weighted MR images (n=40) of the prostate were collected on a 3T GE scanner. Whole gland border delineation was performed manually by two observers. Training of the custom deep learning system was performed on 30 MRI scans using five-fold cross validation with NVIDIA. Needle segmentation was performed on 407 MR images from 54 patients with 3T-MR-guided transperineal prostate biopsy. The needle artifacts were manually segmented by one observer using 3D Slicer from T2-weighted axial MR and then were segmented using NeedleFinder. Results: The trained network achieved Dice scores of 0.88±0.02 and 0.87±0.03 when compared to reference delineations provided by readers. Interobserver agreement between the two readers was 0.88±0.03. NeedleFinder was used to correctly segment 91% of the needles. Each needle was segmented in less 1 second. Conclusion: These automated methods can increase the efficiency and accuracy of image-guided therapy for malignancies of the prostate. Further developments are in progress to eliminate the need for user tip selection.

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

Segmentation of the prostate gland on MRI can facilitate automated fusion of imaging data for targeted biopsy and is important in quantifying PSA density in assessing treatment response which is critical for the dose planning in radiotherapy. Also during an MR-guided prostate biopsy, the actual needle direction can be unavoidably different from the planned needle direction due to tissue structures encountered on the insertion path. In this study, we present the evaluation of a novel fully automatic 3D Slicer extension for whole gland delineation based on artificial intelligent and report a method that rapidly segments the biopsy needle trajectory from MR, and renders it in 3D relative to the target lesion for visualization by the interventional radiologist. The accuracy of the proposed novel automated tool on our clinical data is within the range of inter-reader agreement and is comparable to the results of deep learning methods recently reported by other institutions on different data sets. These automated methods can increase the efficiency, reproducibility, and accuracy of image-guided therapy for malignancies of the prostate. Further developments are in progress to eliminate the need for user tip selection and integrating the automated segmentation into the workflow for navigated biopsies.

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

These automated methods can increase the efficiency/accuracy of image-guided therapy for malignancies of the prostate. Further developments are in progress to eliminate the need for user tip selection and integrating the automated segmentation into the workflow for navigated biopsies.

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