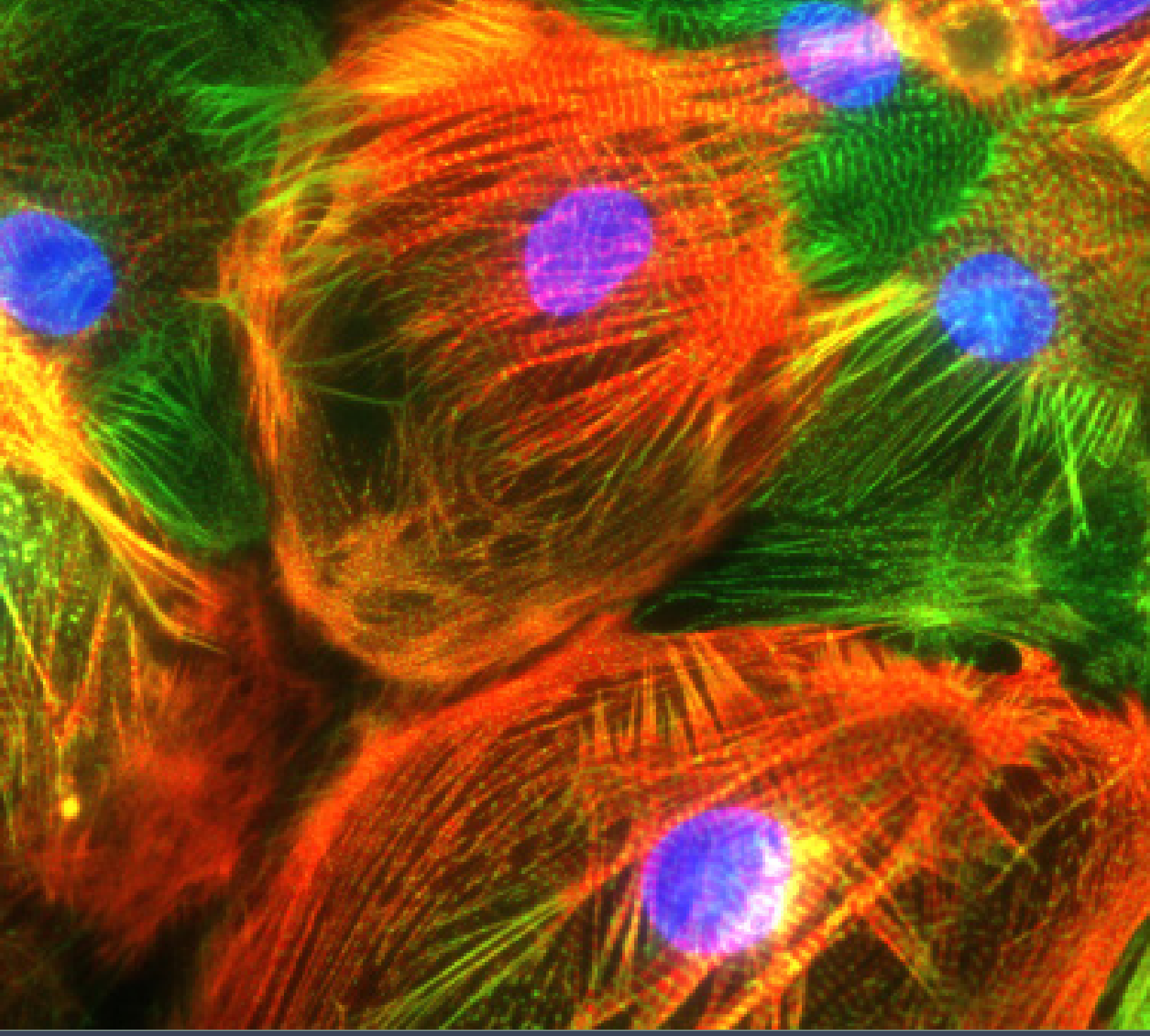

Virtual Poster Session Abstracts

Celebration of SCIENCE

April 6 & 7, 2022

Contents

Agenda

Thursday, April 7, 2022

Celebration of SCIENCE

11:00 am - 1:00 pm	**Virtual Poster Session | Click here to visit the portal**
2:00 - 2:05 pm	**Welcome & Opening Remarks**
2:05 - 2:35 pm	**Celebration of Science & Research at MGH** Merit Cudkowicz, MD, Chair, ECOR
2:35 - 2:45 pm	**Introduction of the Class of 2022 MGH Research Scholars** Susan Slaugenhaupt, PhD, Scientific Director, Mass General Research Institute
2:45 - 3:10 pm	**Howard M. Goodman Fellowship** "Cellular Models of Fetal Neurodevelopment in Maternal Immune Activation" Andrea Edlow, MD, MSc, Assistant Professor of Obstetrics, Gynecology, and Reproductive Biology
3:10 - 3:35 pm	**Howard M. Goodman Fellowship** "Defining the Evolutionary Characteristics of Human Metastasis Across Space and Time" Kamila Naxerova, PhD, Assistant Professor, Radiology, Center for Systems Biology
3:35 - 3:50 pm	**Break**
3:50 - 4:15 pm	**Martin Prize for Clinical Research** "Evolution of Delayed Resistance to Immunotherapy in a Melanoma Responder" Genevieve Boland, MD, PhD, Associate Professor of Surgery
4:15 - 4:35 pm	**Martin Prize for Fundamental Research** "Spatially Organized Multicellular Immune Hubs in Human Colorectal Cancer" Nir Hacohen, PhD, MGH Research Scholar 2012-2017, Professor of Medicine, Cancer Center
4:35 - 5:00	**Martin Prize for Population Health Sciences** "Body-mass index and diabetes risk in 57 low- and middle- income countries: a cross sectional study of nationally representative, individual-level data in 685 616 adults" Jacqueline Seiglie, MD, MSc, Instructor in Medicine, Endocrinology Unit, MGH Center for Global Health

Posters

Bioengineering & Devices

Biomedical Imaging

Cancer

Posters

Posters

Endocrinology

Genetics & Genomics

Posters

Global Health & Infectious Disease

Healthcare and Population Sciences

Posters

Immunology/Inflammation

Neurosciences

Posters

OB / GYN - Women's Health

Posters

Posters

Bioengineering & Devices

Poster Number 1

Anastasia Goulopoulos, BS
Anesthesia, Critical Care and Pain Medicine, Research Technician | agoulopoulos@mgh.harvard.edu

Design optimization of a device for extracorporeal blood phototherapy: light propagation and thermal load analysis

INVESTIGATORS: A. A. Goulopoulos, A. Fischbach, E. Etim, W. Franco, Zapol Lab

The leading cause of poison-related deaths in the United States is carbon monoxide (CO) inhalation. CO binds to hemoglobin (Hb) and displaces oxygen, reducing oxygen delivery to tissues. The optimal treatment for CO poisoning in patients with normal lung function is administering hyperbaric oxygen. However, hyperbaric chambers are only available in medical centers with specialized equipment, resulting in delayed therapy. Visible light dissociates CO from Hb.

In previous studies, we combined a membrane oxygenator with phototherapy using different wavelengths to design a photo-ECMO (extracorporeal membrane oxygenation) device, which improved CO elimination and survival in CO-poisoned animal models.

This work aims to use computational modeling to optimize the design of the photo-ECMO device. In particular, the study focuses on 460 (blue), 532 (green), and 620 (red) nm wavelengths. The deposition of light and the thermal load of blood circulating through the device was calculated using Monte Carlo and heat convection and diffusion models. All wavelengths effectively dissociate CO from Hb and improve CO elimination. However, light at a wavelength of 620 nm penetrates deeper and generates the lowest thermal load.

Hence, further design optimization of photo-ECMO devices should consider light at red wavelengths as the optical source for photodissociation.

Poster Number 2

Mi Ho Jeong, PhD, Pharm.D.
Center for Systems Biology, Research Fellow | mjeong2@mgh.harvard.edu

Plasmon-enhanced analysis of single extracellular vesicles for biliary tract cancer

INVESTIGATORS: M. H. Jeong, T. Son, H. Im

Biliary tract cancer (BTC) is a fatal disease often detected late in unresectable stages. However, there is no effective diagnostic method or biomarkers for early detection of BTC. Analysis of tumor-derived extracellular vesicles (tEVs) provides new opportunities to detect tumor through noninvasive liquid biopsies. Here, we report an advanced nanoplasmonic sensing technology that enables multiplexed single EV analysis with significantly improved detection sensitivity. EVs are captured on the periodic nanodimple surface and immunolabeled for key biomarkers to identify tEVs while the underlying nanodimple structures amplify EVs' fluorescence signals. The plasmon-enhanced EV analysis revealed the heterogeneity of tumor-derived EVs and their marker levels. Furthermore, we identified tumor markers (MUC1, EGFR, and EPCAM) for BTC and applied the marker combination to detect tumor-derived EVs in clinical bile juice samples, which showed 92% detection accuracy, significantly better than conventional clinical parameters. The sensitive and accurate nanoplasmonic EV sensing technology could improve the early BTC diagnosis.

Bioengineering & Devices

Poster Number 3

Kihyeun Kim, PhD
Center for Systems Biology, Research Fellow | kkim50@mgh.harvard.edu
Rapid PCR testing: a lateral flow paper strip with a Joule heater for SARS-CoV-2 detection

INVESTIGATORS: K. Kim, H. Im, M. Kim

Lack of polymerase chain reaction (PCR)-based self-testing kit at home against severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) has impeded to prevent its spread. Here, we demonstrate a rapid PCR test strip by integrating a lateral flow paper chip with a thin-film Joule heater, which enables fast thermocycling without bulky equipment and detects amplified products. Nichrome thin film was used as a Joule heater to achieve stable thermocycling. Fast thermocycling could be achieved using a paper membrane—as a PCR solution container, giving a solution with a high specific surface area. After PCR, amplified products were simultaneously detected at the lateral flow paper chip. As a result, cDNA of SARS-CoV-2 could be detected within 20 min after PCR solution injection, whereas conventional and real-time PCR techniques with bulky equipment took 105 min and 115 min, respectively. Finally, RNA of SARS-CoV-2 was simply detected using our POC PCR paper chip.

Poster Number 4

Kilean Lucas, PhD
Center for Systems Biology, Research Fellow | klucas2@mgh.harvard.edu
Cellular point-of-care diagnostic using an inexpensive layer-stack microfluidic device

INVESTIGATORS: K. S. Lucas, J. Oh, J. Hoelzl, R. Weissleder

Cellular analyses are increasingly used to diagnose diseases at point-of-care and global healthcare settings. Some analyses are simple as they rely on chromogenic stains (blood counts, malaria) but others often require higher multiplexing to define and quantitate cell populations (cancer diagnosis, immunoprofiling). Simplifying the latter with inexpensive solutions represents a current bottleneck in designing start-end pipelines. We reasoned that a simple and inexpensive device could be created by using acrylic pressure sensitive adhesives (PSA) to bond coverslips to a microscopic slide in such a fashion that liquid movement (staining, de-staining, washing) could be performed on chip without the need for an active pump. Indeed, we show that cheap and effective passive pumping layer-stack microfluidics (PLASMIC) can be assembled without the need for special tools. To exchange fluids in PLASMIC devices, the properties of surface tension are exploited using capillary (passive) pumping. By forming droplets of differing sizes on the inlet and outlet of the devices, it is possible to generate sufficient flow in place of an electric pump. In this work, we describe the development, testing, validation, and scale-up of such microfluidic devices for the cyclic imaging of immune and tumor markers. This device allows for reduced reagent consumption and improved imaging reliability. The simple and inexpensive (< $1) device will make single-cell cyclic imaging more accessible to a broad scientific/medical community.

Poster Number 5

Hannah Peterson, PhD
Center for Systems Biology, Research Fellow | hpeterson3@mgh.harvard.edu

Integrated analytical system for clinical single cell analysis

INVESTIGATORS: H. M. Peterson, L. K. Chin, Y. Iwamoto, J. Oh, J. C. Carlson, H. Lee, H. Im, R. Weissleder

High-dimensional analyses of cancers can potentially be used to better define cancer subtypes, analyze the complex tumor microenvironment and perform cancer cell pathway analyses for drug trials. Unfortunately, integrated systems that allow such analyses in serial fine needle aspirates within a day or at point-of-care currently do not exist. To achieve this, we developed an integrated immunofluorescence single-cell analyzer (i2SCAN) for deep profiling of directly harvested cells. By combining a novel cellular imaging system, highly cyclable bioorthogonal FAST antibody panels, and integrated computational analysis, we show that same-day analysis is possible in thousands of harvested cells. We demonstrate that the i2SCAN approach allows comprehensive analysis of breast cancer samples obtained by fine needle aspiration or core tissues. The method is a rapid, robust and low-cost solution to high dimensional analysis of scant clinical specimens.

Poster Number 6

Hyunkyung Woo, PhD
Center for Systems Biology, Research Fellow | hwoo3@mgh.harvard.edu

Characterization and modulation of surface charges to enhance extracellular vesicle isolation in plasma

INVESTIGATORS: H. K. Woo, Y. K. Cho, C. Y. Lee, H. Lee, C. M. Castro, H. Lee

Blood contains different types of bio-nanoparticles that can be exploited for clinical diagnoses. Purifying these particles according to type, however, remains technically challenging. EVs, in particular, are outnumbered >104-fold by low density lipoproteins (LDLs), yet similar in size and density. These fundamental disadvantages often cause LDL spillover into EV isolates, thus confounding assay results. Here, we report that surface charge can be an effective parameter to differentiate EVs from LDLs. By measuring and modeling zeta potentials at different buffer pH, we estimate surface charge densities of EVs (–6.2 mC/m2) and LDLs (–3.6 mC/m2). The analysis reveals that EVs are more negatively charged than LDLs. Furthermore, the charge difference is maximal at a weak acidic condition (pH = 6.4). Building on this finding, we refine an all-in-one chromatography system which performed i) size-exclusion to remove particles smaller than EVs and LDLs and ii) cation-exchange in an acidic elution to retain LDLs longer than EVs. With this, we enrich EVs directly from plasma, depleting >99.8% of LPPs within 30 min. Minimizing LDL contamination improve analytical signal in EV molecular assays, including single vesicle imaging, bulk protein measurements, and mRNA detection.

Poster Number 7

Sangyeon Cho, PhD
Wellman Center for Photomedicine, Research Fellow | scho9@mgh.harvard.edu

Miniaturizing Lasers for Biomedical Analysis and Single Cell Imaging

INVESTIGATORS: S. Cho, Y. Yang, M. Soljacic, S. H. Yun

Fluorescence probes are ubiquitous for bio-labeling and imaging-based assay. Despite their easy usages, however, the quantum nature of fluorescence generates broad emission spectra (linewidth 50~100 nm), limiting their multiplexing to only a handful of resolvable colors. This limited color palette is often a bottleneck in a comprehensive analysis of the single-cell state characterized by various biomarkers. Alternative to fluorescent probes, laser-emitting particles hold a great promise to solve the barrier in multiplexing. Such "laser particles" generate stimulated emission with a linewidth 100 to 1000 times narrower than fluorescence. My lab colleagues and I have worked on this new class of probes and shown a proof of concept for tracking single cells using two micron-sized microlasers with several hundreds of different colors.

Miniaturizing laser particles to the nanoscale is highly desirable because it will minimize perturbation on cellular homeostasis and allow more probes to be inserted into the cytoplasm. However, due to the severe optical losses, lasers remain a few microns in size along the direction of light amplification.
We demonstrated the first sub-micron nanolaser in the visible regime at room temperature, which has a size comparable to the emitted laser wavelength. Our main finding is that attaching metal next to a semiconductor nano-cube can greatly enhance optical resonance and amplification in the submicron structure to generate an ultrasharp laser emission. We are currently making "plasmonic" laser particles compatible with cells and working on applying the nanolasers for bioimaging and single-cell analysis to advance life sciences and medical diagnosis.

Poster Number 8

Felipe Furtado, MD
Radiology, Research Fellow | ffurtado1@mgh.harvard.edu

Simultaneous Multislice Diffusion-weighted Imaging Versus Standard Diffusion-weighted Imaging in Whole-body PET/MRI

INVESTIGATORS: F. S. Furtado, K. E. Suarez-Weiss, T. Vahle, N. D. Mercaldo, M. A. Anderson, A. Mojtahed, O. A. Catalano

BACKGROUND: Diffusion-weighted imaging (DWI) is a magnetic resonance imaging (MRI) sequence useful for diagnosing cancers. However, whole-body (WB) DWI acquisition is lengthy. Simultaneous multislice (SMS) is a parallel imaging implementation that may solve this drawback. This prospective cohort study compared standard (STD) single-shot echo-planar imaging DWI and SMS-DWI during WB positron emission tomography (PET)/MRI regarding acquisition time, image quality, and sensitivity at a lesion level.

METHODS: Subjects with abdominal and/or pelvic neoplasms were enrolled between 8/2018 and 3/2020. Simultaneous PET/MRI was acquired with a 3T Biograph mMR scanner (Siemens, Erlangen, Germany). Subjects underwent standard DWI and SMS-DWI, as well as pre and post-contrast T1-weighted sequences, T2-weighted sequences, and PET, which were the reference standard for lesion detection. Acquisition times were obtained from DICOM timestamps and compared between SMS-DWI and STD-DWI. Image quality and lesion detection for each sequence were evaluated by three board-certified radiologists. Significance was set to $p<0.05$.

RESULTS: Eighty-three adults (47 females, 57%), median age 64 years (IQR 52–71 years), were enrolled. The median WB STD-DWI acquisition time was 14.75 minutes (IQR 14.08–15.96 minutes), compared to 6.95 minutes (IQR 6.67–7.15) for WB SMS-DWI, $p<0.001$. SMS image quality scores were higher than STD within the abdomen (OR 5.31, 95%CI 2.76–10.22, $p<0.001$). Scores were not significantly different in the chest, mediastinum, pelvis, and rectum. STD-DWI detected 277/356 (78%) lesions while SMS-DWI could locate 297 (83%) of them (OR 1.44, 95% CI 1.02–2.01, $p=0.036$).

CONCLUSION: SMS-DWI significantly reduces acquisition time while improving the diagnostic yield.
more effectively predict photosensitivity symptoms in EPP patients than self-reporting of sunlight exposure.

Poster Number 9

Thomas Koch, BS
Ophthalmology, Research Technician | tkoch1@meei.harvard.edu

Comparison between Drusen Volume Calculations in Intermediate Age-related Macular Degeneration on Optical Coherence Tomography (OCT) using Automated vs Manually Adjusted Segmentation and its Association with Retinal Pigment Epithelium (RPE) Bruch's Membrane (BM) Thickness (RPEBMt)

INVESTIGATORS: T. Koch, A. Nigalye, S. Pundlik, G. Tsougranis, R. Katz, I. Garg, H. Wescott, D. Husain, J. B. Miller

Purpose: Drusen burden is a key indicator of age-related macular degeneration (AMD) severity. Real-time manual measurement of drusen volume (DV) by clinicians is not practical. Automated estimates with software save time but are not readily available. We examined the variation with automated vs. manually adjusted retinal layer segmentation between OCT devices.

Methods: Retrospective study of intermediate AMD eyes imaged with Spectralis OCT. Volume scans were processed for automated segmentation to generate drusen volume. To manually adjust segmentation, RPE and BM were fit to demarcation on OCT. Linear regression models with parameters average retinal thickness (RT), DV, and highest RPEBMt were used to associate the RT and DV measurements with the processing method (automated vs. manual), and RPEBMt (continuous measure).

Results: We included 10 eyes of 5 participants. The mean difference between manual and automated processing for RT and DV was 7.9±21.1μm and 0.015±0.04mm3, respectively. Larger differences between manual and automated methods were observed for inner vs. outer macula for both RT (Inner: 12.3±26.6μm; Outer: 2.5±8.4μm) and DV (Inner: 0.017±0.037mm3; Outer: 0.012±0.044mm3). The average of RPEBMt parameter was 85.3±51.9μm. Significant interaction was seen between RPEBMt and processing method for RT (β=0.006,p<0.001) and DV (β=0.007,p<0.001).

Conclusions: Presence of large drusen affected the automated segmentation resulting in larger deviations shown by significant association between RPEBMt, DV, and RT compared to the manual segmentation. Here we show that current automated segmentation does not reliably measure these parameters. There is a need for manual review to mitigate the effects of segmentation errors.

Poster Number 10

Archana Nigalye, MBBS, MD
Ophthalmology, Clinical Research Fellow | archana_nigalye@meei.harvard.edu

Association Between Macular Pigment Optical Density values and Optical Coherence Tomography Parameters in Age-related Macular Degeneration

INVESTIGATORS: A. Nigalye, R. Katz, T. Elze, S. Pundlik, V. P. Douglas, E. S. Lu, G. Tsougranis, I. Lains, M. Kasetty, D. Husain, J. B. Miller

Purpose: Dual wavelength autofluorescence(dwAF) determines macular pigment optical density (MPOD) using blue wavelength absorption by the yellow MP. Association between Heidelberg dwAF MPOD values and OCT parameters in AMD is studied. Methods: Early and intermediate AMD, and controls (> 50 years) underwent dwAF (488 and 514 nm), OCT scans (Spectralis, Heidelberg) and AMD staging using color fundus photographs. The MPOD sum of volume (SoV) calculated within the 1° radius circle around fovea relative to the 6° plateau. Linear mixed-effects regression models used to determine the association of various OCT parameters in AMD with MPOD, accounting for the possible confounders. Results: We included 286 eyes of 161 participants; 201(70%) AMD (19 early, 182 intermediate), and 85 controls (30%). Mean±SD age was 71±9 years, with female (58%), non-smokers (57%), AREDS users (51%). IOL present in 30% AMD eyes and 8% control eyes. OCT abnormalities were absent in the control eyes. In AMD eyes OCT features were, 29% drusenoid pigment epithelial detachment(dPED), 54% central drusen, 41% reticular drusen, 28% hyperreflective foci, and 53% ellipsoid zone disruption. Higher MPOD values were significantly associated with age (β = 6.38, 95% CI: 1.24 – 11.52, p = 0.015), IOL presence (β = 364.01, 95% CI: 268.12 – 459.89, p < 0.001), and the presence of dPED (β = 83.66, 95% CI: 4.93 – 162.39, p = 0.037).Conclusions: The significant association between the MPOD SoV in central 1° radius and the presence of dPED after accounting for confounders, has potential use in determining the role of dual wavelength autofluorescence MPOD as a biomarker in AMD.

Poster Number 11

Yingying Ning, PhD
Radiology, Research Fellow | YNING2@mgh.harvard.edu

Dual lysine aldehyde binding MRI probe for non-invasive in vivo imaging of collagen cross-linking activity in fibrogenesis

INVESTIGATORS: I. Y. Zhou, N. J. Rotile, S. C. Barrett, M. Sojoodi, K. K. Tanabe, J. D. Roberts, B. P. Jackson, H. K. Dresscher, P. Caravan

Fibrosis is a key pathological feature of a majority of diseases including non-alcoholic steatohepatitis, idiopathic pulmonary fibrosis, cancer, myocardial infarction, atherosclerosis, diabetes, Crohn's disease and rheumatoid arthritis. It can affect any organ and is responsible for nearly half of the deaths in the industrialized world. Currently in clinic, there is a lack of non-invasive method to evaluate fibrosis activity in the early stage. Considering that the biochemical features of fibrosis are conserved across tissue and organ types, where dual lysine residues in collagen will be oxidized by lysyl oxidase (LOX) to lysine aldehyde and undergo cross-linking, leading to excess accumulation of extracellular matrix molecules in the parenchyma, we designed a series of gadolinium and manganese-based MRI contrast agents that target lysine aldehyde. From chemistry design to in vivo imaging, we screened a best probe for non-invasive tracking fibrosis activity in disease progression and drug treatment. In vivo enhanced MRI signal showed significant correlation with the change of LOX activity and lysine aldehyde level. We demonstrated the application of this probe in four fibrotic liver models covering mouse, rat and human patient fibrotic tissues. The application of this probe can be further extended to other organ, such as pulmonary and heart fibrosis, showing high potential for translation. For the conserved collagen remodeling mechanics in different tissues and species, the design strategy for targeting dual lysine aldehyde herein also has high potentials to act as a universal diagnosis and treatment target for diverse fibrotic diseases in the future.

https://www.martinos.org/the-centers-yingying-ning-recognized-for-her-work-on-imaging-tissue-fibrogenesis/

Poster Number 12

Mohammad Saad, PhD
Wellman Center for Photomedicine, Research Fellow | msaad1@mgh.harvard.edu

EGFR-targeted multi-modal molecular imaging and photo-immunotherapy of head and neck cancers

INVESTIGATORS: M. A. Saad, L. Contreras, S. Bano, S. Selfridge, Z. Mai, R. Pawle, M. Varvares, S. Mallidi, T. Hasan

Precision molecular imaging finds application in the delineation of tumor margins during surgical resection of head and neck cancers (HNCs). Despite advances in fluorescence guided surgery, there remain challenges in successfully locating tumor margins, resecting the entire tumor volume and treatment of microscopic tumor tissue. The presence of residual tumors, post-surgery, requires additional interventions and if untreated, often leads to tumor recurrence. As Epidermal growth factor receptor (EGFR) is a receptor of choice for targeting in HNCs, this study demonstrates the development of a molecular (EGFR) targeted theranostic probe combining the complementary features of fluorescence and photoacoustic imaging. The probe: DFAC (Dual Function Antibody Conjugate) comprises of a fluorophore/photosensitizer; Benzoporphyrin derivative (BPD) and a photoacoustic contrast agent; naphthalocyanine (NC) derivative conjugated to an EGFR antibody; Cetuximab. While BPD assists in fluorescence imaging, it can also be used for inducing cytotoxicity, through photodynamic activation in target tissues. The efficacy of DFAC in selective visualization and photodynamic therapy of tumor cells is evaluated on heterocellular 3D tumor spheroids and orthotopic mouse tongue tumors developed from human oral cancer cell lines (CAL27 and SCC4), expressing different levels of EGFR. In summary, this study demonstrates the potential of the theranostic probe (DFAC) to delineate tumor regions for guiding surgical resection and eradication of residual tumor tissue, post-surgery, by photo-immunotherapy.

Poster Number 13

Andrew Salvatore, MA
Radiology, Data Analyst | ansalvatore@mgh.harvard.edu

[18F]MK-6240 Test-Retest performance in cognitively normal elderly subjects using PET/MRI

INVESTIGATORS: A. N. Salvatore, J. F. Fu, C. Lois, D. Huell, D. Izquierdo Garcia, A. Garimella, H. Sari, B. Dickerson, K. Johnson, C. Catana, J. C. Price

[18F]MK-6240 is a second-generation tau-PET ligand gaining widespread use. Salinas (JCBFM, 2020) reported Test-Retest variabilities in tau-rich regions for binding potential of 14% and standardized-uptake value (SUV) tissue ratio (SUVR) of 6% for an Alzheimer's disease (AD) subject-dominant sample. We assessed [18F]MK-6240 PET/MRI Test-Retest performance across reference and target regions in a sample largely consisting of cognitively normal elders (eCN). Seventeen participants (4 young-CN (yCN): 28±5 years; 10 eCN: 68±6 years; 3 AD: 58±5 years) underwent [18F]MK-6240 Test PET (0-120 min, ~185 MBq, Biograph-mMR). Eight (7eCN/1AD) also underwent Retest PET within 22±10 days. Four reference regions (REFROIS) and four tau-target regions (TARGETROIS) were examined. Analysis outcomes included SUV90-110 (over 90-110 min) for REFROIS and SUVR90-110 and Simplified Reference-Tissue Model measures of distribution volume ratio (DVR) and relative delivery (R1) for TARGETROIS. Test-Retest variability was computed: T-RT(%)=100*2*|(Test-Retest)|/(Test+Retest).

Here we show that SUV90-110 was similar across REFROIS and groups (0.5-0.7 g/mL), except AD cerebral white-matter was ~2-fold greater. SUV90-110 T-RT was similar across REFROIS (8-10%). Using cerebellar REFROIs, the TARGETROIs SUVR90-110 was 2-3-fold greater for AD than eCN (AD rank-order: Precuneus>Inferior-Temporal>Entorhinal>Hippocam pus; eCN rank-order: Entorhinal>Inferior-Temporal>Precuneus>Hippocampus. The AD DVR rank-order matched SUVR, with Precuneus DVR 2-fold greater than CN DVR (TARGETROIS: 0.89±0.03). AD R1 values (0.51-0.77) were lower than CN (0.58-1.10). TARGETROIs T-RT was 4-8% for SUVR90-110, 3-4% for DVR, and 5-7% for R1 (across REFROIS). These results are consistent with prior reports and provide further evidence of acceptable T-RT in low-signal eCN subjects needed to detect early tau deposition.

Poster Number 14

Riana Schleicher, BS
Neurology, Clinical Research Coordinator | rschleicher@mgh.harvard.edu

Accurate super-resolution low-field brain MRI

INVESTIGATORS: R. L. Schleicher, J. E. Iglesias, B. McKaig, B. Parry, S. Laguna, B. Billot, P. Schaefer, J. N. Goldstein, K. Sheth, M. S. Rosen, W. T. Kimberly

Background: Low-field MRI (LF-MRI) has the potential to transform neuroimaging. However, LF-MRI is limited by lower resolution and signal-to-noise ratio, leading to incomplete characterization of brain regions. To address this challenge, we undertook an extension of a machine learning super-resolution (SR) algorithm to facilitate the synthesis of higher resolution images derived from lower resolution scans.

Methods: This analysis was conducted as part of an ongoing, prospective observational study in the NeuroICU and ED at MGH. Following informed consent, patients underwent LF-MRI scans using a 64mT portable scanner (Hyperfine Swoop). Standard-of-care HF-MRIs were also taken as part of patients' clinical care. In order to evaluate image quality, we applied automated segmentation tools to measure volumes of different brain regions. The HF-MR images were used as targets to train the SR algorithm SynthSR, which was utilized to process the LF-MR T1-weighted and T2-weighted sequences and obtain synthetic 1 mm MPRAGE output.

Results: A total of 11 patients were included in this analysis. Our results show that: (i) application of available automated segmentation tools directly to LF-MRI images falters; but (ii) segmentation tools succeed when applied to SR images with high correlation to gold standard measurements from HF-MRI (e.g., r=0.85 for hippocampal volume, r=0.84 for the thalamus, r=0.92 for the whole cerebrum).

Conclusions: This work demonstrates proof-of-principle post-processing image enhancement from lower resolution LF-MRI sequences. These results lay the foundation for future work to enhance the detection of normal and abnormal image findings at LF and ultimately improve the diagnostic performance of LF-MRI.

Poster Number 15

Amal Tiss, PhD
Radiology, Research Fellow | atiss@mgh.harvard.edu

Impact of motion correction on longitudinal [18F]-MK6240 tau PET imaging

INVESTIGATORS: A. Tiss, T. Marin, K. Gong, C. Lois, Y. Chemli, Y. Petibon, V. Landes, K. Grogg, M. Normandin, M. Spangler-Bickell, A. Becker, E. Thibault, K. Johnson, G. El Fakhri, J. Ouyang

Positron Emission Tomography (PET) imaging of tau deposition using [18F]-MK6240 involves long acquisitions in older subjects, many of whom exhibit dementia symptoms. The resulting unavoidable head motion can greatly degrade image quality thus requiring motion correction (MC). Motion increases variability of PET quantitation across subjects which in turn requires larger sample sizes in clinical trials. We apply a list-mode based motion correction method to longitudinal studies in 51 subjects (45 cognitively normal, 4 with mild cognitive impairment, 2 with Alzheimer's disease (AD)) and evaluate its effect on estimated standardized uptake value ratio changes (ΔSUVR) in key brain regions. We evaluate the impact of MC on the statistical power of a hypothetical clinical trial.

Here we show that 26% of the individual scans exhibited notable motion, affecting 39% of the longitudinal datasets (motion in one or both time points). MC reduced the standard deviation of ΔSUVR across subjects by -44%, -17%, -13%, and -19% in the entorhinal, inferior temporal, precuneus, and amygdala regions, respectively. In a hypothetical clinical trial, an annualized increase of 10% in the entorhinal region is assumed. To detect a 25% reduction in the rate of tau uptake after administrating a candidate drug, the sample size needed decreased from 1500 to 468 with motion correction.

Motion is a major confounding factor in [18F]-MK6240 PET imaging. Motion correction can reduce the variance in estimated ΔSUVR, potentially allowing for shorter inter-scan time and smaller sample size in clinical trials evaluating the effect of a candidate drug against AD.

Poster Number 16

Gregory Tsougranis, BA
Ophthalmology, Graduate Student | gtsougranis@meei.harvard.edu

Optical Coherence Tomography (OCT) Features Associated with Three-Year Changes in Microperimetry Sensitivity in Age-related Macular Degeneration (AMD)

INVESTIGATORS: G. H. Tsougranis, K. Mendez, I. Laíns, A. Nigalye, R. Katz, T. Koch, J. Lasky-Su, I. K. Kim, D. G. Vavvas, J. B. Miller, J. W. Miller, D. Husain

Purpose: Retinal sensitivity measured by microperimetry may be a more sensitive measure of disease progression than standard visual acuity in patients with dry age-related macular degeneration (AMD). Several optical coherence tomography (OCT) structural parameters have been associated with decreased retinal sensitivity in AMD. However, limited longitudinal work has been published to date. This study aimed to evaluate associations between baseline OCT structural parameters and changes in average retinal sensitivity over three years.

Methods: Prospective, longitudinal study. At baseline and 3 years later, AMD patients and controls were imaged with color-fundus photographs and OCT. OCT features were graded by two independent graders and MAIA microperimetry was used to assess retinal sensitivity. Multivariable and univariable mixed-effect linear regression models were utilized for data analysis.

Results: We included data from 43 eyes with AMD and 22 eyes from age-matched controls. A diagnosis of early AMD at baseline was associated with decreased average retinal sensitivity three years later (p=.03). Accounting for confounding factors, the presence of ellipsoid disruption was associated with decreased average retinal sensitivity at three years (p= .04, b= -5.33).

Conclusions: Here we show that among several OCT features commonly seen in patients with AMD, the presence of ellipsoid zone disruption at baseline was associated with a decrease in average retinal sensitivity at three years. These results support retinal sensitivity measured by MAIA microperimetry as a potentially useful functional measure in the care of patients with AMD. Longitudinal structure/function correlations like these may improve our ability to provide prognostic information in AMD.

Poster Number 17

Jingting Yao, PhD
Radiology, Research Fellow | jyao0@mgh.harvard.edu

Moving MRI: Imaging a Moving Body with a Moving MRI Magnet

INVESTIGATORS: N. Patel, J. Yao, A. Kaso, A. Van der Kouwe, Y. C. Chen, P. Le, D. Merfeld, J. L. Ackerman. This project is supported by NIH BRAIN Initiative grant 1R01EB029818.

Imaging during natural large-scale motion of the body, such as testing a vestibular dysfunction patient using natural motion stimuli, could provide critical information for studying motor control and vestibular function. Conventional functional magnetic resonance imaging (fMRI) measures neuronal activation while both the magnet and the subject are stationary. This project introduces moving magnetic resonance imaging (mMRI), presenting one implementation of this technology. We designed a mechanical system to tilt a magnet safely and steadily. Moving the magnet concurrently with the subject minimizes motion artifacts and magnetic field-induced physiological effects while providing high-quality anatomic and functional imaging. The mMRI employs a dedicated inexpensive, compact, cryogen-free extremity MRI scanner. Because this magnet is liquid cryogen-free and conduction-cooled, it may be moved while energized. Subsequent effort focuses on demonstrating anatomic and functional mMRI in phantoms, and a pilot study using live rats. This lays the foundation for the ultimate goal of developing and validating a human-scale prototype mMRI system in which the magnet and the subject together undergo substantial motion (rotations, translation, and tilts) while remaining stationary with respect to each other. This would be the first system to enable measuring high-quality anatomic and functional MR images in subjects experiencing naturalistic motions. The outcome of this work is likely to advance our knowledge in traumatic brain injury (by imaging how the brain moves in response to external forces), cardiovascular regulation, sensorimotor integration, and sensory conflict. All of these conditions involve situations with large-scale bodily motion which cannot be accommodated in conventional MRI.

Poster Number 18

Joelle Al Hokayem, BS, MD
Neurology, Research Fellow | JELHOKAYEM@mgh.harvard.edu

A Promising Novel Therapeutic Agent to Overcome Diffuse Intrinsic Pontine Glioma

INVESTIGATORS: B. A. Tannous

Diffuse Intrinsic Pontine Glioma (DIPG) is an aggressive tumor in the brainstem which controls the body's vital functions, making it the leading cause of death from pediatric brain tumors. Due to its infiltrative nature, complete surgical removal of the tumor is not possible while radiotherapy showed minimal effect. DIPG is underserved with a desperate need for novel therapeutic agents. Using patient-derived DIPG cells, we performed a repurposing drug screen and identified that a subset of quinoline class anti-malaria agents, including mefloquine, to have significant DIPG killing properties. Mefloquine crosses the blood-brain barrier (BBB), thus has an advantage for DIPG, but is known to cause adverse neurological effects. By shifting these adverse effects in favor of a potential therapeutic advantage, a more potent drug that serves as an analog at low dose, would achieve the desired concentration to halt DIPG growth. In their search for antimalarial drugs with lower toxicity, researchers at the Walter Reed Army Institute of Research (WRAIR) have amassed a large collection of structurally diverse quinoline analogs. To identify analogs with improved efficacy, we performed a quantitative structure-activity relationship on this drug library and identified several compounds to kill DIPGs at lower concentrations. We selected 2-TQM which showed enhanced efficacy against all DIPG cells tested. 2-TQM did not show any signs of toxicity but lead to a decrease in tumor growth and improved survival. Given its characteristics in penetrating the brain and strong efficacy, our results suggest 2-TQM as a promising therapeutic against DIPGs and warrant clinical investigation.

Poster Number 19

Amelia Cogan, MPH
Medicine, Clinical Research Coordinator | ascogan@mgh.harvard.edu

Oncology Patients with Platin Hypersensitivity Reactions Can Safely Receive First-Line Chemotherapy through Risk Stratification and Desensitization: An Academic Institution's 3-Year Experience

INVESTIGATORS: A. S. Cogan, A. E. McMahon, B. R. Slawski, A. Banerji

Chemotherapy hypersensitivity reactions (HSR) impact care and are concerning to patients. Management varies depending on the culprit drug(s), existing collaboration between oncology and allergy, and allergist experience with desensitization. In less optimal scenarios, oncologists may opt for alternative, potentially less effective chemotherapeutics in patients after HSRs. Alternatively, most oncology patients can safely proceed with first-line chemotherapy despite a HSR with allergy consultation, risk stratification, and desensitization, when necessary. Desensitization uses gradually increasing doses of an allergen to induce a temporary period of tolerance. We sought to describe our institution's experience using risk stratification and safety of desensitization after HSR to platinum-based chemotherapeutics (platins) when indicated. We performed a retrospective chart review of patients at Massachusetts General Hospital who initiated desensitization to a platin between January 1, 2018, and December 31, 2020. 138 patients, including 80 oxaliplatin (58%), 48 carboplatin (35%), and 10 cisplatin (7%), underwent 707 desensitizations. The majority were female (n=88, 64%) and white (n=109, 79%). 100 (73%) patients had initial HSRs grade 2 or higher using Ring and Messmer classification. Most desensitizations (n=587, 83%) were associated with no reaction or cutaneous symptoms only (grade 1). Among 194 (27%) HSRs during desensitization, 120 (62%) were grade 2 or higher. Only 9 (1%) desensitizations in 8 patients were not completed due to severe allergic reactions (6), concern for infection (1), side effects of sedating medications (1), and hemolytic reaction (1). Our experience shows that desensitizations allow oncology patients to safely receive first-line chemotherapeutic treatment despite a platin HSR.

Poster Number 20

Scott Ferguson, PhD
Radiology, Research Fellow | sferguson6@mgh.harvard.edu

Single EV analysis (sEVA) of mutated proteins allows detection of stage 1 pancreatic cancer

INVESTIGATORS: S. W. Ferguson, K. S. Yang, P. Zelga, A. S. Liss, J. Carlson, C. Fernandez del Castillo, R. Weissleder

Tumor cell derived extracellular vesicles (EV) are being explored as circulating biomarkers for cancer detection. Up to now however, clinical results have been mixed for a number of reasons including the predominant use of bulk measurements, the inability to differentiate tumor from host cell derived vesicles, the general absence of uniquely identifying biomarkers and the unknown frequency of stochastically distributed biomarkers into single circulating vesicles. We hypothesized that a single EV analysis (sEVA) technique could potentially improve diagnostic accuracy necessary to detect early cancers but the actual biomarker frequency and practical detection limits are currently unknown. Using pancreatic cancer, we carefully analyzed the composition of putative cancer markers in 11 established and new patient derived models. In parental PDAC cells positive for KRASmut and/or P53mut proteins only ~40% of EVs were also positive (range: 30-64%). This rate of positivity increased to 57% when additional PDAC biomarkers were considered (MUC1, EGFR, αFG-P40H) in cell lines. In a blinded study involving 16 patients with surgically proven stage 1 PDAC, KRASmut and P53mut protein was detectable at much lower levels, generally in < 0.1% of vesicles. With the analytical capabilities of sEVA however, 15 of the 16 patients with stage 1 PDAC expressed low levels of biomarker positive EV. Using a modeling approach, we estimate that the current PDAC detection limit is at ~0.1 cm3 tumor volume, below clinical imaging capabilities. These findings establish the potential for single EV analysis for early cancer detection.

Poster Number 21

Renata Fleming, PhD
Neurology, Research Fellow | rfleming2@mgh.harvard.edu

Characterization of Neuropeptide Profile in Glioblastoma Cancer Stem Cells: Are Neuropeptide a Key Factor for Resistance?

INVESTIGATORS: R. Fleming, B. Tannous

Glioblastoma (GBM) is the most common and aggressive type of malignant brain tumor in adults. Despite multimodal treatment, including surgical resection, radiation, and temozolomide chemotherapy, tumor tend to recur due to a subpopulation of stem-like cells (GSCs) also responsible for therapeutic resistance. There is a great effort to better understand the oncobiology of GBM and overcome tumor resistance. GBM grows in a rich neurochemical milieu, but the impact of neurochemicals on gliomagenesis is largely unexplored. Neuropeptides are a group of signaling messengers that function as neurotransmitters, paracrine regulators, and hormones to regulate exocrine and endocrine secretion and inflammation. Neuropeptides have also been recognized as potent cellular growth factors for many cell types, including cancer. Based on the regulatory function of neuropeptides, we hypothesized that neuropeptides could be involved in GSCs intercellular communication and therapeutic resistance. Here, we characterized for the first time the neuropeptide profile in different GBM molecular subtypes, including pro-neural (PN; better prognosis) and mesenchymal (MES; worse prognosis) and investigated their role in GSCs therapeutic resistance. We found a differentially expressed neuropeptide profile in the different GSCs subtypes. VGF in particular was upregulated in MES subtype compared to the PN subtype. Knockdown of VGF decreased GSCs proliferation and sensitized them to temozolomide therapy. Altogether, neuropeptides could be one of the milieu factors linked to GBM plasticity and provide a new target for adjuvant therapy.

Poster Number 22

Connor Geraghty, PhD
Medicine, Research Fellow | cgeraghty@mgh.harvard.edu

The Impact of Immunotherapy on the Gut Microbiome of Cancer Patients

INVESTIGATORS: A. T. Chan, D. A. Drew, T. S. Hong, C. Huttenhower

Background: Combination neoadjuvant immunotherapy is a promising strategy for the treatment of gastrointestinal cancers. The role of the gut microbiome as a determinant of immunotherapy response has received much interest, yet the specific longitudinal impact of immunotherapy on the gut microbiome is poorly understood.

Study Design: We prospectively collected fecal samples from patients undergoing combination anti-CTLA-4 and anti-PD-1 immunotherapy (Ipilimumab and Nivolumab) with adjuvant radiotherapy throughout the treatment course. We performed shotgun metagenomic sequencing with bioinformatic processing through the bioBakery 3 workflows. This included KneadData for quality control and MetaPhlAn 3 for taxonomic assignment.

Results: Using 39 samples from 7 patients, we assessed the influence of immunotherapy on both overall gut microbiome configuration and on individual taxa throughout treatment. Compared to pre-treatment samples, immunotherapy significantly reduced microbial richness (α-diversity, paired t-test, $p<0.05$) and may moderately alter relative abundance of individual species. Immunotherapy, in combination with radiotherapy, led to perturbations in microbial communities during the treatment time course compared to pre-treatment samples.

Conclusions: Cancer treatment has modest effects on overall microbial community structure, yet our small set of radio/immunotherapy patients suggest that one or more individual microbes might be perturbed, and these changes persist through treatment cycles. Studies are ongoing to examine whether these longitudinal changes are associated with patient prognosis, including the incidence of immunotherapy toxicities. By improving our understanding of the temporal dynamics of individual microbiomes throughout cancer treatment, adjuvant approaches targeting stabilization of the gut microbiome may be developed to improve immunotherapy efficacy or other patient-related outcomes.

Poster Number 23

Anushka Ghosh, BS
Radiation Oncology, Clinical Research Coordinator | aghosh3@mgh.harvard.edu

Racial, Ethnic, and Geographical Differences in Testicular Cancer Mortality Trends in the United States

INVESTIGATORS: A. Ghosh, S. Goldberg, F. Chino, J. A. Efstathiou, S. C. Kamran

Background
Incidence rates of Testicular cancer (TC) have been slowly increasing in the United States in recent decades. Given that TC has a diverse presentation, this study aimed to establish racial, ethnic, geographical differences in longitudinal mortality trends.

Methods
Age-adjusted cancer mortality rates for TC were obtained for men in the United States from the CDC Wide-ranging Online Data for Epidemiologic Research database. Testicular cancer-specific mortality (TCSM) rates from 1999-2019 were calculated using linear regression. Trends in mortality by race, ethnicity, urbanization, and census region were analyzed using SAS 9.4. TCSM rates were compared by F-test. A two-sided hypothesis test was performed for p-values, where values < 0.05 were considered statistically significant.

Results
From 1999-2019, overall age-adjusted TCSM has been slowly increasing annually (p=NS). There was worsening TCSM rates for Hispanics (+)0.0019/100,000/year compared to non-Hispanics (-)0.003; p=0.010. Black men had slightly improved TCSM rates/year (-0.0007) compared to White men (+0.0006); p=0.049. Significant geographical differences were observed, with a decreasing TCSM rate of (-)0.00092 the Northeast and an increasing rate of (+)0.00086 in the West (p = 0.032 for difference between slopes). Among urbanization categories, TCSM rates in Large Central Metros regions (population > 1 million) and Small Metro regions (population 50,000-249,999) were significantly different [(-)0.0004 and (+)0.0022 respectively; p =0.048]. All other comparisons were not significant.

Conclusion
Mortality rates from TC have been increasing, particularly among Hispanics, with significant racial and geographical disparities. Understanding racial, ethnic, and geographical trends in TCSM rates is important in reducing deaths caused by TC.

Poster Number 24

Toshiro Hara, PhD
Pathology, Research Fellow | THARA2@mgh.harvard.edu

Interactions between cancer cells and immune cells drive transitions to mesenchymal-like states in glioblastoma

INVESTIGATORS: T. Hara, R. Rony Chanoch-Myers, N. D. Mathewson, C. Myskiw, L. Atta, L. Bussema, S. W. Eichhorn, A. C. Greenwald, G. S. Kinker, C. Rodman, L. N. Castro, H. Wakimoto, O. Rozenblatt-Rosen, X. Zhuang, J. Fan, T. Hunter, I. M. Verma, K. W. Wucherpfennig, A. Regev, I. Tirosh, M. L. Suva

Glioblastoma is the most common and lethal form of intracranial tumor, with no effective treatment available. Despite the growing awareness that extensive molecular and cellular heterogeneity in glioblastoma is a major impediment for successful therapy, how to overcome the heterogeneity remains unexplored. To comprehensively characterize such glioblastoma heterogeneity, we previously used an integrative approach, combining single-cell RNA-seq (scRNA-seq) of 28 patient samples and patient-derived xenografts (PDX), with analysis of 401 TCGA bulk glioblastoma specimen. We found that malignant cells in glioblastoma exist in a limited set of four cellular states that recapitulate (1) neural progenitor-like (NPC-like), (2) oligodendrocyte-progenitor-like (OPC-like), (3) astrocyte-like (AC-like) and (4) mesenchymal-like (MES-like) states. Among the four recurrent cellular states, three states recapitulate neurodevelopment, while the origin of the fourth state—resembling mesenchymal cells—remains poorly understood.

Here we dissect glioblastoma-to-microenvironment interactions by scRNA-seq analysis of human tumors and model systems, combined with functional experiments. We demonstrate that macrophages induce a transition of glioblastoma cells into mesenchymal-like (MES-like) states. This effect is mediated, both in vitro and in vivo, by macrophage-secreted Oncostatin M (OSM) that interacts with OSMR or LIFR (in complex with GP130) on glioblastoma cells, thereby activating STAT3. We show that MES-like glioblastoma states are associated with increased abundance and cytotoxicity of tumor-infiltrating T and potentially with better clinical response to immunotherapies. Overall, our work dissects the cellular interactions within the glioblastoma microenvironment, with potential implications for therapies.

Poster Number 25

Roshani Jha, BS
Neurology, Research Technician | rjha4@mgh.harvard.edu

Divergent MEK/ERK and AMPK signaling dictates plasticity and vulnerability to fatty acid synthesis inhibitors in glioblastoma stem-like cells

INVESTIGATORS: R. Jha, K. M. Eyme, A. Sammarco, R. J. Neustadt, H. Mnatsakanyan, C. Moses, A. Alnasser, D. Tardiff, C. Y. Chung, C. E. Badr

Understanding and generating effective therapies for glioblastoma, an incurable and fatal brain cancer, is essential. Recent literature has implicated de novo lipid synthesis (DNLS) with glioblastoma as a means for cancer cells to adapt and proliferate in harsh microenvironments. Therefore, DNLS serves as a vulnerability that can be targeted for drug therapy once the molecular mechanisms that define its susceptibility to treatment are elucidated. We have previously shown that stearoyl-CoA desaturase (SCD), an essential enzyme for fatty acid desaturation, is required for glioblastoma stem cell (GSC) self-renewal and that it is a therapeutic target in glioblastoma. Here, we report that YTX-7739, the first clinical-grade, blood-brain barrier penetrant inhibitor of SCD effectively prevents fatty acid desaturation and promotes lethal lipotoxicity in GSCs. Consequently, mice models of glioblastoma implanted with GSCs benefited from this drug therapy and showed extended survival, confirming preclinical efficacy of the drug. Importantly, we reveal that the susceptibility of the GSCs to DNLS inhibition, and particularly SCD inhibition, depends on aberrant MEK/ERK signaling and repression of the nutrient-sensor AMP-activated protein kinase (AMPK). Conversely, AMPK activation confers cryoprotection against lipotoxicity, and promotes a metabolic adaptation which renders GSCs impervious to DNLS inhibition. Altogether, our findings reveal predictive biomarkers of therapeutic response to DNLS-targeted therapies and provide a framework for rational and effective integration of YTX-7739 with conventional treatment of patients diagnosed with glioblastoma.

Poster Number 26

Taïsha Joseph, BS
Cancer Center, Bioinformatics Analyst | tjoseph6@mgh.harvard.edu

Impaired replication stress response mechanisms in non-cancerous breast tissues of BRCA2 mutation carriers.

INVESTIGATORS: T. V. Joseph, M. Karaayvaz-Yildirim, R. E. Silberman, A. Langenbucher, S. V. Saladi, K. N. Ross, E. Zarcaro, A. Desmond, M. Yildirim, V. Vivekanandan, H. Ravichandran, R. Mylavagnanam, M. C. Specht, S. Ramaswamy, M. Lawrence, E. Rheinbay, A. Amon, L. W. Ellisen

Individuals with the BRCA2 heterozygous germline mutations (BRCA2mut/+) have an approximately 70% increased risk of developing certain types of cancers, including breast cancer. BRCA1 and BRCA2 are protein-coding genes that are involved in DNA damage repair. While many studies have investigated the genomic alterations in cancerous breast tissues of BRCA1/ BRCA2mut/+ in comparison to normal tissue, little is still known about early patterns of genomic alterations, prior to the onset of histological abnormalities, in the tissues of BRCA mutation carriers. In this poster, I present the published results from whole genome sequencing analysis and bulk RNA-sequencing of non-cancerous breast tissues from BRCA2mut/+ and wildtype (WT) controls. Our findings reveal the presence of polyclonal sub-chromosomal copy number variations (CNVs) in the breast epithelia of BRCA2 mutation carriers, with the luminal progenitor (LP) cells harboring significantly more CNVs than the basal compartment (P=0.04). Comet assays of freshly sorted epithelial cells showed significantly more DNA damage in the cells of BRCA2mut/+ compared to WT at both baseline and following induced replication stress via treatment with hydroxyurea (HU). This indicates ongoing DNA damage and deregulated DNA damage response in the breast epithelia of BRCA2mut/+. These findings strongly suggest haploinsufficiency in the breast epithelia of BRCA2mut/+ patients as a potential early event in the course of breast cancer formation. The results from this study may provide further insight into the early mechanisms underlying the pathogenesis of BRCA-derived breast cancer.

Poster Number 27

Ashwin Kumar, BEng
Cancer Center, Graduate Student | askumar@mgh.harvard.edu

Addition of losartan to FOLFORINOX and chemoradiation downregulates pro-invasion and immunosuppression-associated genes in locally-advanced pancreatic cancer

INVESTIGATOR: A. S. Kumar, S. Subudhi, Y. Boucher, L. Gu, I. X. Chen, M. R. Ng, M. Mino-Kenudson, N. Talele, D. G. Duda, D. Fukumura, J. E. Murphy, J. Y. Wo, J. W. Clark, D. P. Ryan, C. Fernandez-Del Castillo, T. S. Hong, R. K. Jain

Purpose: A phase II trial in patients with locally-advanced pancreatic cancer (LAPC) revealed unprecedented rates of complete surgical resection after adding losartan to FOLFIRINOX (FFX) chemotherapy followed by chemoradiation (CRT). The aim of the current study was to identify potential mechanisms of benefit by assessing the effects of FFX-losartan+CRT and FFX+CRT on the stromal tumor microenvironment.
Experimental Design: We performed a gene analysis of RNA extracted from pancreatic cancer tissue sections and immunohistochemistry for immune cells using surgical samples from patients treated with FFX+CRT, FFX-losartan+CRT or underwent surgery upfront without any neoadjuvant therapy.
Results: Neoadjuvant FFX-losartan+CRT and FFX+CRT increased the expression of genes linked to vascular normalization, the transendothelial migration of leukocytes, T cell activation, cytolytic activity and dendritic cell-related genes. In comparison to FFX+CRT, FFX-losartan+CRT downregulated immunosuppression, pro-invasion and M2 macrophage-related genes, and upregulated genes involved in T cell activation.
Our immunohistochemistry results revealed that FFX-losartan+CRT improved the intratumoral infiltration of CD3+/CD8+ T cells and reduced regulatory T cells in PDAC lesions with a complete/near complete response. Furthermore, we found significantly less residual disease in lesions treated with FFX-losartan+CRT versus FFX+CRT.
For FFX-losartan+CRT treated patients, overall survival was positively correlated with genes linked to the transendothelial migration of leukocytes, angiogenesis and tumor suppression, and inversely correlated with genes that play a role in invasion and metastasis.
Conclusions: Our findings suggest that adding losartan to FFX+CRT reduces pro-invasion effects and immunosuppression in PDAC microenvironment, which is associated with improved T cell infiltration/activity and treatment outcome in patients with LAPC.

Poster Number 28

Heena Kumra, PhD
Radiation Oncology, Research Fellow | hkumra@mgh.harvard.edu

IL-1 blockade prevents cardiac toxicities and improves efficacy of immunotherapy in mouse pancreatic cancer

INVESTIGATORS: N. P. Talele, H. Kumra, I. L. Gomes-Santos, S. Roberge, W. W. Ho, P. Andersson, S. Chatterjee, M. Siwicki, D. G. Duda, M. J. Pittet, D. Fukumura, R. K. Jain, Pancreatic Cancer Microenvironment Network: PaCMEN

Background: Immune checkpoint blockers (ICBs) have revolutionized cancer treatment, but they are often associated with severe immune related adverse events (irAEs). These get further exacerbated in patients with high body-mass index (BMI), and/or concomitantly treated with cytotoxic therapy.

Aim/Hypothesis: We aimed to understand the mechanism of ICB-induced irAEs and how they get aggravated with high BMI and combination drug therapy.
Methods: We developed a clinically relevant mouse model of cardiac irAEs that combines: (i) a difficult-to-treat cancer (pancreatic ductal adenocarcinoma; PDAC), (ii) high-fat diet induced high BMI, and (iii) a combination treatment including ICBs and chemotherapy.
Results: We show that mice with orthotopic PDAC and fed a high-fat diet developed irAEs after treatment with ICBs (α-PD1 + α-CTLA4) and chemotherapy (FOLFIRINOX) as compared to chow diet. These irAEs recapitulated the phenotype observed in patients with cancer and obesity, including cardiac dysfunction consistent with myocarditis, cardiac fibrosis, and increased circulating levels of interleukin-1 beta (IL-1b). Mechanistically, we identified a causal involvement of IL-1b in the promotion of irAEs, as its blockade prevented myocarditis and reduced cardiac fibrosis after immunotherapy. Importantly, IL-1b blockade also enhanced the anti-tumor effects of ICB + FFX combination therapy, and increased mouse survival.
Conclusions: Using a translationally relevant mouse model, we discovered a role for IL-1b in ICB-induced cardiotoxicity, which is the most fatal type of irAE in cancer patients. In addition, we found that IL-1b blockers, which are already used in the clinic, may both reduce adverse events and enhance the ant-itumor effects triggered by immunotherapy.

Poster Number 29

Pin-Ji Lei, PhD
Radiation Oncology, Research Fellow | plei3@mgh.harvard.edu

Single cell analysis of breast cancer lymph node metastasis reveals cancer cell plasticity and MHC class II-mediated immune regulation

INVESTIGATORS: P. Lei, E. Pereira, P. Andersson, Z. Amoozgar, J. W. Van Wijnbergen, S. Chatterjee, W. W. Ho, J. M. Posada, H. Zhou, A. S. Kumar, C. Chuang, I. Ergin, D. Jones, P. Huang, S. Beyaz, T. P. Padera

Tumor-draining lymph nodes are often the first site of metastasis and lymph node metastases are associated with worse prognosis. Using a mouse model of breast cancer that develops spontaneous lymph node metastasis, we performed high-resolution single-cell RNA sequencing of primary tumors and metastatic lymph nodes (metLNs) to measure how cancer cells adapt to the lymph node microenvironment. Single-cell trajectory analysis suggests a mesenchymal-to-epithelial transition of cancer cells in metLNs. Further, the epithelial-like cancer cells in metLNs expressed high levels of genes encoding MHC class II molecules (MHC-II). Cancer cells in metLNs from breast cancer patients also exhibited MHC-II as shown by immunohistochemistry and single-cell analysis. Interferon-gamma signaling mediates the induction of MHC-II in cancer cells. Interestingly, co-stimulatory molecule expression was absent in MHC-II positive cancer cells. Additionally, we found an increase in Ctla4, Foxp3, Il2ra (CD25), Tnfrsf18 (GITR) and Ikzf2 (Helios) positive regulatory T cells (Tregs) in metLNs compared to naïve lymph nodes. In human breast cancer metLNs, we also observed the elevation of TNFRSF18 (GITR), IKZF2 (HELIOS) and MAF in Tregs, suggesting an enhanced immunosuppressive characteristic. Our data leading to the hypothesis that the absence of co-stimulatory signals on MHC-II positive cancer cells induces CD4+ T cell anergy and the expansion of Tregs in the metLNs. Testing this hypothesis in vitro showed a decrease in CD4+ effector cells and an increase in Tregs in the presence of 4T1 cancer cells. These data provide the basis for new opportunities to therapeutically stimulate anti-cancer immune responses.

Poster Number 30

Mao Li, PhD
Neurology, Graduate Student | mli36@mgh.harvard.edu

Olfactory Receptor 5B21 Drives Breast Cancer Metastasis Via EMT Through NF-κB/STAT3/CEBPκ Signaling

INVESTIGATORS: B. A. T

Olfactory receptors (ORs), the largest GPCR family member, have been found expressed in nonolfactory sites and played an essential role in various physiological processes, including cancer. In this study, we focus on the expression and function of ORs in breast cancer. A metastatic breast cancer model has been established by intracardiac injection of MDA-MB-231 (231P) cells in immunocompromised mice followed by producing of three derivative cell lines from developed metastatic sites including the brain-seeking clone (231BR), the bone-seeking clone (231BO), and the lung-seeking clone (231LM). The difference expressed ORs between metastatic breast cancer cells and primary breast cancer cells have been identified and OR5B21 displays a high expression in all metastatic cells. Knockdown of OR5B21 significantly decreases the invasion and migration of breast cancer cells as well as metastasis to different organs, while overexpression of OR5B21 displays the opposite effect. Mechanistically, OR5B21 expression is associated with epithelial to mesenchymal transition through the STAT3/NFkB/CEBPʙ signaling axis. We propose OR5B21 (and potentially other ORs) as a novel oncogene contributing to breast cancer (brain) metastasis and a potential target for adjuvant therapy.

Poster Number 31

Semer Maksoud, PhD
Neurology, Research Fellow | smaksoud@mgh.harvard.edu

Development of a PROTAC degrader capable of penetrating the blood-brain barrier and targeting the oncoprotein BRD4 in glioblastoma multiforme.

INVESTIGATORS: S. Maksoud

Glioblastoma (GBM) is the most malignant form of primary brain tumors in adults with a 5-year survival rate of <10%. Standard-of-care treatment involves maximal surgical resection followed by radiation and chemotherapy; however, these treatments have not been effective in preventing disease progression. These tumors are characterized by a diffusive infiltration of tumor cells, cellular heterogeneity, and the presence of glioma stem-like cells (GSCs), a cellular subset capable of significantly expanding and generating new tumors. We have previously identified the natural product obtusaquinone (OBT) as a potent antineoplastic agent with promising in vivo activity against gliomas. Based on the observation that OBT binds Keap1 and induces its proteasomal degradation, we hypothesized that OBT could be exploited as a novel ubiquitin ligase recruiting moiety for the design of proteolysis-targeting chimeras (PROTACs), a technology that engages the ubiquitin-proteasome system to remove disease-causing proteins. We synthesized a chimera consisting of OBT and JQ1 separated by a linker. JQ1 is a well-established PROTAC ligand and a selective inhibitor of BRD4, an important regulator of glioma growth. Our results show that OBT-JQ1 has a more pronounced cytotoxic effect in GSCs when compared to OBT or JQ1, either individually or in combination. More importantly, OBT-JQ1 is brain penetrant and active in vivo, delaying tumor growth, increasing the survival of treated mice, and inducing the degradation of BRD4 in vivo as well as in cell cultures. These results position OBT-JQ1 as a candidate molecule for the development of next-generation therapies against gliomas, and possibly other types of cancer.

Poster Number 32

Varvara Mazina, MD
Obstetrics and Gynecology, Clinical Research Fellow | vmazina@mgh.harvard.edu

High loss of heterozygosity is frequent among high-risk, microsatellite stable endometrioid and serous endometrial tumors.

INVESTIGATORS: V. Mazina, B. Rueda, E. Eisenhauer, A. Bregar, J. Watkins, L. Philp, S. Johnstone, W. Growdon

Objective: To analyze loss of heterozygosity (LOH) profiles in a subset of high-risk endometrial tumors and correlate these findings with mismatch repair deficiency (dMMR), microsatellite instability (MSI), tumor mutational burden (TMB) and programmed-death ligand 1 (PD-L1) expression.

Methods: With IRB approval, we identified a cohort of 51 archival tumor specimens of high grade endometrioid or serous carcinoma of the uterus. MMR status and clinical data was collected by retrospective chart review. Expression of PD-L1 was determined by IHC. Samples were sent to Foundation Medicine for next-generation sequencing (NGS) to evaluate for MSI, LOH, and TMB. Differences in proportions were evaluated by the Fisher's exact test using SAS statistical software.

Results: NGS data was available for 49 of the submitted 51 tumor samples. The median age of patients in the cohort was 69 (range 30-85). High grade endometrioid tumors were significantly more likely to have high TMB compared to serous tumors (45.4% vs 12.5%, p=0.01), while a similar proportion were found to have high LOH (25% vs 19%, p=0.48). Among microsatellite stable tumors with available LOH data, the rate of high LOH was 25% (8 of 32 tumors), compared to none of the MSI-high tumors (0 of 7; p = 0.15).

Conclusions: High LOH was frequently seen among microsatellite stable / MMR-proficient tumors in this high-risk cohort. LOH should be evaluated in high-risk tumors without microsatellite instability and treatment approaches combining PARP-inhibition and immunotherapy should be explored in order to improve response to immunotherapy in this patient population.

Poster Number 33

Hayk Mnatsakanyan, PhD
Neurology, Research Fellow | hmnatsakanyanmovsesyan@mgh.harvard.edu

SCD5 protects Glioblastoma stem cells from death and differentiation by modulating intracellular lipid composition

INVESTIGATORS: H. Mnatsakanyan, R. J. Neustadt, A. Sammarco, C. E. Badr

Glioblastoma (GBM) is the most common malignant brain cancer in adults. It is highly aggressive, incurable, and resistant to therapy. Despite surgical resection of tumor tissue and chemotherapy, a small subpopulation of GBM stem cells (GSC) can survive and drive tumor recurrence and therapeutic resistance. Considerable evidence suggests that the endogenous levels of unsaturated fatty acids (FA) are crucial regulators of cancer stem cell survival and self-renewal. Stearoyl-CoA desaturase-1 (SCD-1) is the most abundant desaturase in humans. We have previously shown that SCD1 activity is required for cancer stem cells self-renewal and brain tumor initiation. However, SCD1 orthologous isoform, SCD5, has been poorly characterized and its potential role in GBM has not been previously reported. We have observed that SCD5 is highly enriched in both GSC and neural stem cells (NSC). We saw that GSC differentiation triggered by BMP4 results in a strong downregulation of most fatty acids biosynthesis enzymes, including SCD5. Genetic downregulation of SCD5 led to a remarkable decrease in stem cell markers in GSC and NSC, and impaired cell viability exclusively in GSCs. Downregulation of SCD5 in GSCs orthotopically implanted in mice resulted in delayed tumor growth and extended overall survival. Finally, using shotgun lipidomics in GSCs after genetic downregulation of SCD1 or SCD5 revealed a largely distinctive lipidome profile further highlighting a divergent role of these two isoforms in GBM lipid metabolism. Altogether, our results underscore a novel function of SCD isoforms in GSCs metabolism and highlight SCD5 as a potential therapeutic target for GBM.

Poster Number 34

Satoru Morita, MD, PhD
Radiation Oncology, Research Fellow | smorita@mgh.harvard.edu

Increased CD8+ T-cell infiltration and efficacy for multikinase inhibitors after PD-1 blockade in HCC

INVESTIGATORS: S. Morita, H. Kikuchi, A. Matsui, Z. Amoozgar, K. Inoue, Z. Ruan, D. Staiculescu, J. S. Wong, P. Huang, T. Yau, R. K. Jain, D. G. Duda, Edwin. L. Steele Laboratories for Tumor Biology

The recent revolution in HCC treatment––brought about by the development of novel immunotherapies and anti-angiogenic therapies (kinase inhibitors, antibodies), alone or in combination––has highlighted the promise as well as the limitations and challenges of these interventions. Immune checkpoint blockade combined with anti-angiogenic therapy induces vascular normalization and anti-tumor immunity and is efficacious. However, prolonged therapy with these agents in combination has the risk of high systemic and financial toxicities, and the response to treatment, while impressive, remains transient in most patients. A new strategy to address these major clinical problems in HCC management, particularly the optimal therapeutic sequence, is urgently needed. But whether and how initial immunotherapy affects the efficacy of subsequent anti-angiogenic therapy is unknown. We evaluated a cohort of HCC patients who received the pan-VEGF receptor multi-kinase inhibitor sorafenib after initial therapy with an anti-programmed cell death protein (PD)-1 antibody and found superior outcomes in these patients. To confirm this benefit, we examined the impact of an anti-PD-1 antibody on response to subsequent sorafenib and understood the mechanisms of action, and we tested this treatment sequence in orthotopic and autochthonous models of murine HCC. We found that prior anti-PD-1 antibody treatment amplified HCC response to sorafenib therapy and increased survival. Anti-PD-1 therapy showed angio-protective effects on HCC vessels to subsequent sorafenib treatment, which enhanced the benefit of combination therapy in a CD8+ T-cell-dependent manner. Here we show this priming approach using immunotherapy provides an immediately translatable strategy for more effective treatment of HCC while reducing drug exposure.

Poster Number 35

Markus Schweiger, MS
Neurology, Graduate Student | mschweiger@mgh.harvard.edu

Friend and Foe: Radiation Therapy Modulates Glioblastoma Immune Evasion via Extracellular Vesicles

INVESTIGATORS: M. W. Schweiger, Z. Amoozgar, B. A. Tannous

Glioblastoma (GBM) is the most common form of malignant primary brain tumor and despite optimal treatment, long-term survival remains incredibly rare. Radiation therapy (RT) leads to successful initial tumor regression but recurrence is inevitable. Previous studies have shown that ionizing radiation changes the composition of the tumor microenvironment and alters the expression of immune-related markers on tumor cells. Extracellular vesicles (EVs) are vesicular bodies of cellular origin and secreted by nearly every cell. They have been shown to carry a variety of cargo (DNA, proteins, RNAs, lipids) which can be taken up by other cells. Notably, previous studies highlight that EVs drive GBM progression and immune evasion by acting as multifunctional signaling complexes.

Here we show that ionizing radiation of GBM cells results in an altered EV secretome and further facilitates the uptake of EVs in recipient cells. In addition, EVs secreted by GBM cells following radiation modulate the tumor microenvironment by manipulating the innate as well as the adaptive immune response. We dissected a novel mechanism by which GBM evades the immune system with the help of EVs following RT, pointing towards novel therapeutic strategies to prevent GBM recurrence.

Poster Number 36

Emma Siefring, BA
Psychiatry, Clinical Research Fellow | esiefring@mgh.harvard.edu

A Multi-Step Approach to Adapting a Mind-Body Resiliency Intervention for Fear of Cancer Recurrence and Uncertainty in Survivorship (IN FOCUS)

INVESTIGATORS: E. Siefring, Z. Mian, R. Li, G. Yeh, C. O'Cleirigh, J. Peppercorn, L. Wagner, J. Denninger, A. Bullock, H. Mizrach, B. Goshe, T. Cheung, A. Markowitz, E. Park, D. Hall

Background: For cancer survivors, there is a paucity of scalable, fear of recurrence (FOR) interventions that integrate empirically supported mind-body and psychological skills for managing FOR.

Objective: Adapt an evidence-based resiliency intervention (SMART-3RP) to address FOR among cancer survivors.

Methods: A team of researchers, clinicians, and cancer survivors followed an iterative intervention adaptation process (ORBIT). First, we defined FOR management skills through a literature review and feedback from patients. Second, we integrated findings into a treatment manual and refined procedures for delivery to groups of cancer survivors. Third, we conducted a single arm trial to assess acceptability and change in FOR severity with 23 cancer survivors (N=4 intervention groups). Fourth, we conducted additional qualitative interviews with 28 cancer survivors (N=6 focus groups stratified by FOR severity, N=15 individual interviews) to define strategies for coping with FOR and to identify preferences for delivery. Fifth, we refined the treatment manual and procedures for testing in a future pilot randomized feasibility trial.

Results: The adapted protocol includes content on FOR and healthcare engagement. The single arm trial suggested preliminary feasibility and reductions in FOR severity, yet need for refinement, prompting additional qualitative interviews for further targeting. The resulting intervention (IN FOCUS) is a virtual, synchronous, group program that offers an integrated approach to FOR management by teaching stress management and resiliency training skills.

Conclusions: IN FOCUS is a novel intervention for FOR in cancer survivors that teaches mind-body resiliency skills. We are now conducting a feasibility randomized trial.

Poster Number 37

Swati Sonal, MBBS
Surgery, Research Fellow | ssonal1@mgh.harvard.edu

Molecular basis of Extramural Vascular Invasion (EMVI) positive Colorectal Carcinoma

INVESTIGATORS: S. Sonal, V. Deshpande, D. Ting, J. C. Cusack, A. R. Parikh, A. Neyaz, A. Pankaj, M. Taylor, A. M. Dinaux, L. G. J Leijssen, C. Boudreau, H. Kunitake, R. N. Goldstone, L. G. Bordeianou, R. Ricciardi, C. E. Cauley, D. L. Berger

Extramural Vascular Invasion (EMVI) is a known poor prognostic factor in Colorectal Carcinoma. However, its molecular basis has not been well defined. Our aim in this study is to assess the expression of immune and molecular markers in EMVI positive Colorectal Carcinoma to understand their tumor microenvironment.

Immunohistochemistry was performed on tissue microarrays of surgical pathology specimens obtained from Colorectal Cancer patients operated at our institution. Automated quantification was used for CD8, LAG3, FOXP3, CD163 & manual quantification was used for PD-L1, HLA I markers (Beta-2 Microglobulin, HC10) and HLA II. Dual staining for PDL1-PU1 represented tumor-associated macrophages.

There were 300 EMVI positive and 687 EMVI negative tumors. PDL1 was barely expressed on tumor cells throughout the entire cohort. There was a significantly lower expression of CD8 ($p=0.009$), LAG3 ($p=0.03$), FOXP3 ($p<0.0001$), PU1 immune cells ($p=0.0004$), PDL1 positive macrophages ($p<0.0001$), and Beta-2 Microglobulin on tumor cells ($p=0.003$) in the EMVI positive tumors when compared to the EMVI negative tumors. When looking at chemo naïve tumors, LAG3 ($p=0.04$), FOXP3 ($p=0.001$), PU1 immune cells ($p=0.04$), PDL1 positive macrophages ($p=0.0001$), and Beta-2 Microglobulin on tumor cells ($p=0.01$) also had significantly lower expression in EMVI positive tumors.

Here we show that there is blunting of the immune response in EMVI positive tumors compared to EMVI negative tumors in Colorectal Carcinoma which may contribute to their poor prognosis.

Poster Number 38

Dominique Zarrella, BS
Obstetrics and Gynecology, Laboratory Technologist | dzarrella@mgh.harvard.edu

Ovarian Cancer Stem Cell Populations Respond Differently to Inhibition of EZH2 Action

INVESTIGATORS: D. Zarrella, R. Xu, C. Shimada, K. Cowden-Dahl, B. Rueda

Enhancer of zeste homolog 2 (EZH2) protein is involved in trimethylation of lysine 27 of histone H3 (H3K27me3) which disrupts the cell cycle resulting in increased proliferation, metastasis, and angiogenesis. EZH2 is elevated in 50-80% of ovarian cancer (OvCa) and correlates with poor overall survival. Previously, we demonstrated that PARP inhibitors (PARPi) enrich for ovarian cancer stem cells (CSCs). Here, we assess how disruption of EZH2 action affects CSC populations alone or in combination with PARPi or carboplatin. We treated OvCa cell lines (A2780, OVCAR4) with vehicle(s), single-agent EZH2 inhibitor GSK-126, carboplatin, olaparib, and combinations of GSK-126 with carboplatin or olaparib. Endpoints included cell proliferation/survival, H3K27 trimethylation status, and flow cytometry for CD133 levels and ALDH activity (CSCs markers). GSK-126 reduced H3K27 trimethylation indicating on-target effects. GSK-126 reduced the metabolic activity of OvCa cells compared to carboplatin ($p\leq 0.0002$) while GSK-126 and carboplatin combined was more effective at reducing metabolic activity than either single agent ($p<0.0001$). Using flow cytometry, we observed that treatment with either PARPi or carboplatin enriched for CSC populations ($p\leq0.0034$) whereas EZH2 inhibition enriched for CD133 positive cells but decreased the number of cells with high ALDH1 high activity. Combining GSK-126 and PAPRi or carboplatin negated the CSC enrichment but did not impact baseline levels. These data suggest that EZH2 disruption negatively impacts ALDH active cells but promotes CD133 positive cells. Combining GSK-126 with carboplatin or PARPi negates the increase in CD133 positive populations suggesting a possible method for reducing CSC populations that contribute to recurrence.

Poster Number 39

Hengbo Zhou, PhD
Radiation Oncology, Research Fellow | hzhou20@mgh.harvard.edu

Immune checkpoint blockade efficacy is not reliant on direct Tumor draining lymph nodes

INVESTIGATORS: H. Zhou, P. J. Lei, M. O'Melia, T. P. Padera

Sentinel lymph node biopsy (SLNB) is commonly performed in the clinic to stage patients and determine a treatment course. Complete LN dissection (CLND) is also used in high-risk patients to avoid relapse and metastasis. Due to the importance of LNs in adaptive immunity, it is imperative to evaluate the effects of SLNB and CLND on immune checkpoint blockade (ICB) efficacy as removing tumor draining lymph nodes (TDLNs) that are encountering the most tumor antigen might stunt anti-cancer immune responses. Recent work has demonstrated that PD-1/PD-L1 interaction and tumor-specific T cells are enriched in TDLNs, but not in non-TDLNs. Intrapleural delivery of low-dose PD-L1 antibody (ab) to TDLNs can induce greater anti-tumor immunity, compared to a systemic approach. These data suggest removal of TDLNs might impair ICB outcome. Indeed, anti-PD-1 or anti-4-1BB efficacy can be abolished by TDLN dissection in subcutaneously grafted colon cancer models. However, resected stage III melanoma patients can still respond and benefit from ipilimumab or nivolumab treatment, indicating ICBs can still have an effect after TDLN removal. Here, by using breast cancer and melanoma orthotopic models, we demonstrate that neither SLNB nor CLND diminishes ICB efficacy or immune memory, regardless of whether the resection was conducted pre-emptively or post-tumor establishment, similarly to the clinical data Mechanistically, we discovered that, after TDLN resection, antigen can be transported to distal LNs through remodeled lymphatic vessel drainage and blood circulation, which contributes to the residual responsiveness to ICB. Thus, ICB efficacy is not reliant on the presence of direct TDLNs.

Poster Number 40

Jacqueline Dron, PhD
Center for Genomic Medicine, Research Fellow | JDRON@mgh.harvard.edu

Lifelong protection against coronary heart disease from loss-of-function variants in APOB and PCSK9

INVESTIGATORS: J. S. Dron, A. P. Patel, Y. Zhang, D. Maamari, M. Wang, A. E. Moran, G. M. Peloso, P. Natarajan, A. V. Khera, Lipids Working Group of the NHLBI TOPMed Program

Low-density lipoprotein (LDL) cholesterol-lowering effects and protection against coronary heart disease (CHD) conferred by loss-of-function (LOF) variants in the APOB and PCSK9 genes have not been fully investigated. Here we evaluate how LOF variants in these genes impact lifetime LDL cholesterol trajectories and their associated protection against CHD in large-scale prospective study cohorts. In participants from the NHLBI Trans-Omics for Precision Medicine (TOPMed) Program, whole-genome sequencing data were screened for LOF variants in APOB and PCSK9 and LDL cholesterol trajectories were imputed for ages 18 to 99 using multi-visit clinical data. Additionally, UK Biobank participants with whole-exome data, clinical variables, and cardiovascular-related outcomes were used to establish lifetime risk for CHD between LOF variant carriers and non-carriers. From the TOPMed study cohorts (N=28,252), 146 participants (0.52%) were identified as carriers for a LOF variant. Imputed lifelong LDL cholesterol trajectories revealed carriers were exposed to 37.5% lower cumulative LDL cholesterol and had a 51% lower CHD risk compared to non-carriers (HR 0.49 [95% CI 0.28-0.86]; P=0.01). From the UK Biobank (N=200,455), 696 participants (0.35%) were identified as carriers for a LOF variant. Modeling lifetime CHD risk showed carriers had a 51% lower CHD risk compared to non-carriers (HR 0.49 [95% CI 0.31-0.78];P=0.002). Here we show that effects from APOB and PCSK9 LOF variants are apparent early in life, and the reduced cumulative LDL cholesterol exposure confers substantial, lifelong protection against CHD.

Poster Number 41

Rebecca Freeman, BA
Anesthesia, Critical Care and Pain Medicine, Research Technician | rnfreeman@mgh.harvard.edu

The cardioprotective role of FAM3D in myocardial ischemia reperfusion injury through regulating inflammation

INVESTIGATORS: R. Freeman, J. Rhee, D. Zlotoff, K. Roh, C. Xiao, H. Li, S. Guseh, A. Kuznetsov, N. Houstis, J. Roh, F. Damilano, J. Guerra, X. Liu, R. Shah, M. Silverman, R. Kwong, S. Das, A. Rosenzweig

Myocardial infarction (MI), followed by ischemia-reperfusion injury (IRI), is one of the leading causes of heart failure (HF). However, the determinants of beneficial "reverse" remodeling versus adverse remodeling after MI are unclear, as even initial infarct size is not a perfect predictor. In this study, patients were matched by their initial infarct size, and then stratified as either "Good" or "Poor" remodelers, a metric defined by the overall improvement or deterioration, respectively, of their left ventricular dilation six months after MI. Proteomics analysis of patient plasma, taken at 4 weeks post-MI, revealed that the secreted molecule FAM3D is significantly increased within the "Good" remodeler cohort. FAM3D is thought to bind to formyl-peptide receptors (FPR), which are primarily expressed on immune cells. Interestingly, after myocardial IRI in mice, cardiac FPR1 and 2, as well as splenic FAM3D, are all significantly upregulated. Furthermore, exogenous FAM3D, either as purified recombinant protein or adenovirally encoded protein, dramatically reduces infarct size 24 after reperfusion. In vitro, FAM3D attenuates inflammation in rodent cardiomyocytes independent of any immune cell signaling. Based on these results, FAM3D likely has multiple roles in preserving myocardial health and function after MI.

Poster Number 42

Aditya Jain, BS
Medicine, Graduate Student | adityajain@hms.harvard.edu

Sex-based differences in coronary artery morphology, disease distribution, and lesion outcomes

INVESTIGATORS: P. Di Achille, E. V. Pomerantsev, J. M. Garasic, P. T. Ellinor, A. A. Philippakis, A. C. Fahed, Division of Cardiology, Department of Medicine, Massachusetts General Hospital

Coronary artery disease remains the leading cause of death in men and women. Understanding sex-based differences in coronary artery morphology, disease distribution, and lesion outcomes could help guide decisions on lesion treatment and management.

In a retrospective cohort of 40,766 patients who underwent coronary angiography at the Massachusetts General Hospital, we show coronary morphology and lesion distribution differed by sex. Compared to females, males were more likely to have lesions in distal/branch segments than in proximal/mid segments (relative risk 1.16, 95% CI 1.13-1.18). Males were more likely to have left or mixed dominance (17.6% vs. 15.6%, $p<0.001$), and left main trifurcation (10.5% vs. 5.5%, $p<0.001$). Left or mixed dominance decreased the odds of obstructive disease by 12.5% ($p<0.001$) after adjusting for age and sex.

In 1,276 patients with serial angiograms, 832 of 2,187 (38.0%) baseline obstructive lesions did not require future intervention, and 288 of 2,388 (12.1%) baseline non-obstructive lesions required future intervention. After adjusting for age, sex, and stenosis severity, lesion location strongly predicted future need for intervention. For example, distal LAD was protective (odds ratio: 0.48, 95% CI 0.27-0.82) while proximal (OR: 5.52, 95% CI 2.44-6.68) and mid LAD (OR: 6.85, 95% CI 5.07-9.29) increased odds of intervention. On the contrary, proximal (OR: 3.37, 95% CI 2.44-4.68), mid (OR: 3.45, 95% CI 2.49-4.79), and distal RCA (OR 3.24, 95% CI 2.14-4.90) locations increased risk uniformly.

Significant sex-based differences in coronary artery morphology, location, and disease distribution exist and their interplay may inform future need for intervention.

Poster Number 43

Alexandra Kuznetsov, BA
Medicine, Research Technician | akuznetsov1@mgh.harvard.edu
Understanding Regulatory Pathways of Cardiac Regression

INVESTIGATORS: A. Kuznetsov, J. S. Guseh, B. Atlason, A. Rosenzweig

Heart failure (HF) is a leading cause of death in the US. A key clinical insight is that cardiac hypertrophy commonly precedes HF. Studies suggest that even modest reversal of cardiac hypertrophy (cardiac regression) provides substantial benefits. To understand the transcriptional program behind cardiac regression, we examined four models. First, we performed RNA-seq on Burmese Python hearts, which provide an extreme model of postprandial cardiac hypertrophy followed by complete regression. We also examined three murine models of myocardial regression: (1) a pressure overload-aortic debanding model, (2) a 17-hour fast model and (3) a model of heart failure induced by Activin over-expression. mRNA sequencing of these samples revealed several insights. First, principal component analysis revealed distinct myocardial growth and regression states along the first principal component (PC1), explaining 31.4% of transcriptomic variation. Second, the regression states were heterogeneous, suggesting that regression might have beneficial and adverse forms. Third, we examined the 2461loadings of PC1 and identified genes that distinguish growth and regression; these included structural genes associated with growth (ACTA1) in the growth set and genes associated with regression (FBX032) in the regression set. Finally, Gene Set Enrichment Analysis identified overrepresented pathways in PC1. Gene sets enriched in regression included lipid homeostasis (ES=0.57, p=0.02) and Wnt signaling (ES=0.45, p=0.02), while those associated with growth included mitotic spindle assembly (ES=0.99, p=0.006). These data reveal conserved transcriptional genes associated with myocardial regression across vertebrate species. Future studies that regulate regression pathways offer therapeutic promise for cardiac hypertrophy and heart failure.

Poster Number 44

Aatira Vijay, PhD
Medicine, Research Fellow | avijay@mgh.harvard.edu
Acetylsalicylic acid Accelerates Murine Stasis Venous Thrombus Resolution, Independent of Sex

INVESTIGATORS: A. Vijay, Y. Kawamura, M. Kassab, A. Mauskapf, K. Ha, J. McCarthy, K. R. McCrae, P. K. Henke, F. A. Jaffer

The lack of a stasis venous thrombosis (VT) model in female mice has limited investigation on sex differences in anti-VT therapies, such as acetylsalicylic acid (ASA), which appears efficacious in recurrent VT. Here we (i) develop a new extended stasis VT model; and (ii) examine the effects of ASA on stasis VT resolution in both female and male mice. To extend stasis thrombus persistence, femoral vein was ligated, followed by a second ligation of saphenous vein, below popliteal vein. Following FITC-dextran injection (10 mg/kg), FITC light irradiation (475/35nm, 20x) for three minutes across three illumination fields generated stasis VT. Dylight649-GPIbʙ was injected (100ug/kg, ex 630nm) to observe platelets. At T30', FTP11-CyAm7 (150nmol/kg, ex 750 nm) was injected for fibrin. ASA pre-treatment was done for 7 days (3mg/kg, n=5-6). IVM images were acquired (90i, NIS Elements software, Nikon). Double ligation (DL) thrombus was significantly larger than single ligation (SL) and remained so through 24h and 48h. Corresponding sections of thrombus showed a persistent core consisting of platelets and fibrin. In DL, females developed reproducible stasis VT burden and resolution profiles as in males. ASA pre-treatment resulted in reduced thrombus (T0'), and accelerated resolution in both sexes. ASA inhibited platelet recruitment to thrombi within T30', consistent with its known anti-platelet effect via irreversible inhibition of Thromboxane A2. Here, we established an extended stasis VT model applicable to both female and male mice which is amenable to study vein wall fibrosis. ASA inhibits thrombus formation and accelerates thrombus resolution in a sex-independent manner.

Poster Number 45

Yirong Zhou, MD, PhD
Center for Systems Biology, Research Fellow | yzhou47@mgh.harvard.edu

Cardiac intravital microscopy enables quantitative mapping of capillary-level blood flow in the murine heart

INVESTIGATORS:Y. Zhou, K. R. King, A. D. Aaron

Introduction: Coronary microvascular disease (CMD) is increasingly appreciated as a contributor to adverse cardiovascular outcomes, but underlying mechanisms of CMD remain poorly understood. Investigation of CMD in animal models is limited by a lack of techniques to quantify flow in the heart. We assessed the hypothesis that intravital microscopy (IVM) can enable in vivo imaging of red blood cell (RBC) flow profiles in the coronary microcirculation at cellular resolution. Methods: C57BL/6 mice (n=20) were used to develop cardiac IVM protocols. Cardiomyocyte membrane staining was achieved using intravenous injection of di-2-anepeq. RBC labeling was done by ex-vivo staining of cells with Ter119 followed by transfusion. IVM was performed through a thoracotomy with animals anesthetized and ventilated. Confocal and two-photon microscopy was done using a custom tissue stabilizer and an Olympus FV1000MPE microscope synchronized to physiologic signals using custom hardware and software and cardiac pacing protocols. Images were analyzed in MATLAB to extract myocyte contractile properties, capillary diameter, and capillary flow properties. Results: Using cardiac and respiratory gating, images with cellular resolution could be measured in the beating heart at all phases of the cardiac cycle. This enabled quantification of cardiomyocyte contractile function and capillary diameter and widefield imaging by stitching of several images. Tracking of RBCs over serial images allowed quantification of RBC velocity across multiple capillaries simultaneously. Conclusion: Cardiac IVM can provide quantification of cardiac function and blood flow at the single cell scale and will provide an exciting tool for investigating CMD in models of heart disease.

Poster Number 46

Amity Eaton, PhD
Medicine, Research Fellow | aeaton7@mgh.harvard.edu

V-ATPase Domain Assembly is Increased in Ncoa7 KO Mice

INVESTIGATORS: A. F. Eaton, M. Merkulova, D. Brown

The kidney V-ATPase, or proton pump, is expressed in intercalated cells (ICs), which regulate acid-base homeostasis by adjusting V-ATPase activity. Critically, for proton pumping to occur, the V-ATPase domains must assemble into a functional holoenzyme, which must be trafficked to the apical plasma membrane. Thus, V-ATPase dysfunction in ICs leads to distal renal tubular acidosis (dRTA).

We found that Ncoa7 interacts with the IC-specific B1 isoform of the V-ATPase. Importantly, Ncoa7 knockout (KO) mice developed dRTA. Here, we asked whether Ncoa7 deletion affected trafficking or assembly of the V-ATPase. Wild type (WT) and Ncoa7 KO mice were injected with CPT-cAMP, to stimulate proton secretion, or saline, as a control. B1 and a4 subunit localization was visualized in ICs by immunofluorescence and apical accumulation was quantified by line intensity scanning. Our results show that cAMP significantly increased apical accumulation of B1 and a4 in controls, as expected. However, ICs in the Ncoa7 KO mice were highly activated at baseline, with a trend towards increased apical accumulation of the V-ATPase after cAMP treatment. A Pearson's analysis of B1 and a4, as a measure of V-ATPase assembly, revealed a significant increase in colocalization in Ncoa7 KO mice, relative to control animals. Furthermore, a Proximity Ligation Assay showed a marked increase in assembly in untreated Ncoa7 KO ICs compared to controls.

Thus, we conclude that Ncoa7 is part of a regulatory mechanism that inhibits assembly of the V-ATPase into a holoenzyme in WT mice, while not affecting trafficking of V-ATPase to the apical surface.

Poster Number 47

Allison Fisher, PhD
Medicine, Research Fellow | afisher7@mgh.harvard.edu

Functional role of endothelial transferrin receptor 1 in iron sensing and homeostasis

INVESTIGATORS: A. L. Fisher, C. Y. Wang, Y. Xu, X. Xiao, G. Moschetta, J. L. Babitt

BIron homeostasis is regulated by the hormone hepcidin to balance meeting iron requirements while limiting toxicity from iron excess. Iron induces the production of bone morphogenetic proteins (BMP) 6 and BMP2, which activate hepcidin expression. Liver endothelial cells (LECs) are the main source of BMP ligands, but how LECs sense iron levels to modulate BMP transcription is uncertain.

We investigated the mechanisms of endothelial iron sensing using in vitro and in vivo models. We developed an in vitro model using primary LEC cultures and found that LECs take up the main form of iron in plasma, transferrin-bound iron, resulting in induction of Bmp6 expression. In contrast, Bmp6 expression was suppressed by iron chelation, suggesting that intracellular iron regulates Bmp6 expression. Knockdown of transferrin receptor 1 (TFR1) in LECs blunted transferrin-iron uptake and Bmp6 induction, suggesting a functional role of TFR1 in iron sensing. We generated mice with endothelial-specific ablation of Tfr1 and evaluated their iron phenotype. Mice lacking Tfr1 had altered iron homeostasis when fed a low iron diet, as evidenced by increased liver iron, but lower Bmp6 and hepcidin expression. We did not observe any iron phenotype in mice fed iron-rich standard diet, suggesting that other transporters are dominant when iron availability is high. Indeed, treatment of primary LECs with non-transferrin bound iron or ferritin increased Bmp6 expression, and the underlying mechanisms are under investigation.

Our data demonstrate a functional role of TFR1 in endothelial iron sensing and hepcidin regulation when iron availability is limited.

Poster Number 48

Victoria Jiang, MD
Obstetrics and Gynecology, Clinical Research Fellow | vjiang2@mgh.harvard.edu

The Use of Voting Ensembles and Patient Characteristics to Improve the Accuracy of Deep Neural Networks as a Non-Invasive Method to Classify Embryo Ploidy Status

INVESTIGATORS: M. K. Kanakasabapathy, P. Thirumalaraju, H. Kandula, I. Souter, C. L. Bormann

OBJECTIVE: To determine if creating Voting Ensembles with Convolutional Neural Networks (CNN), Support Vector Machines (SVM), and multi-layer neural networks (NN) with clinical parameters can improve the accuracy of Artificial Intelligence (AI), as a non-invasive method to predict aneuploidy.

MATERIALS/METHODS: A CNN was trained, validated, and tested using 699 Day 5 blastocysts with known results for preimplantation genetic testing for aneuploidy (PGT-A). All embryos were analyzed using FAST-SeqS next-generation sequencing (Invitae). Patient characteristics such as maternal age, AMH level, paternal sperm quality (1-4: 1=Poor, 4=Excellent), and total number of normally fertilized (2PN) embryos were collected and processed using SVM and NN. To improve model performance, we created Voting Ensembles using CNN, SVMs, NNs to combine our EmbryoScope data with clinical parameters. One-tailed t-tests were performed for clinical significance.

RESULTS: CNN alone had a test accuracy of 61.19% (± 1.32%; SEM, n=3 models) in correctly classifying euploid/aneuploid embryos despite patient characteristics (n=140 embryos). When the CNN model was assessed as a voting ensemble, the test accuracy improved when incorporating clinical parameters to 65.0% (AMH, p=0.1), 66.42% (maternal age, p=0.06), 65.71% (maternal age, AMH; p=0. 08), 66.42% (maternal age, AMH, number of 2PNs; p=0.06), and 71.42% (maternal age, AMH, number of 2PNs, sperm quality, p=0.02) (n=140 embryos).

CONCLUSIONS: By combining image based CNNs with patient characteristics, voting ensembles can be created to improve the accuracy of classifying embryos as euploid/aneuploid from CNN alone, showing the potential for AI to serve as a non-invasive method to aid in karyotype screening of embryos.

Poster Number 49

Shriyaa Mittal, PhD
Center for Computational and Integrative Biology, Research Fellow | mittal@molbio.mgh.harvard.edu

Insights into the catalytic structure and metal-ion coordination of the nonenzymatic RNA copying reaction center

INVESTIGATORS: S. Mittal, J. W. Szostak

An efficient pathway for nonenzymatic RNA copying begins with the reaction of two activated monomers to generate an imidazolium-bridged dinucleotide. The bridged dinucleotide binds to the template RNA strand via canonical base pairing, next to a primer strand. Crystal structures have been unable to resolve the orientation of the imidazolium moiety on the bridged dinucleotide, the coordination geometry of a metal ion in the reaction site, and do not provide any insight into the structural dynamics. To characterize the optimal geometry for primer O3′ attack on the bridged dinucleotide, we performed atomistic molecular dynamics simulations of primer/template/dinucleotide/helper oligomers RNA complexes. By comparing our simulations with two bridged dinucleotide orientations we identify the catalytically favorable conformation. Like most catalytic RNA, magnesium ions have been thought to play an important role in RNA copying. In this work, we examined potential magnesium ion contacts with multiple oxygen atoms in the reaction center. Through our simulations, we predict the preferred coordination of the catalytic magnesium ion between the last primer nucleotide and the imidazolium-bridged dinucleotide. We also observe the stabilization of the reaction center and the entire RNA complex in the presence of the magnesium ion. Our findings provide an important role for the bridging magnesium ion in overcoming electrostatic repulsion between an unprotonated O3′ and the phosphate group of the bridged dinucleotide.

Poster Number 50

Sophia Shalhout, PhD
Medicine, Research Fellow | sshalhout@mgh.harvard.edu

eLAB: A Large-Scale Laboratory Integration EHR-R-REDCap Informatics Pipeline for Clinical Research

INVESTIGATORS: S. Z. Shalhout, D. M. Miller, Project Data Sphere

Objective: To develop a clinical informatics pipeline designed to capture large-scale, structured EHR data for a national patient registry.

Materials and Methods: The EHR-R-REDCap pipeline is implemented using R-statistical software to remap and import structured EHR data into the REDCap-based multi-institutional Merkel Cell Carcinoma (MCC) Patient Registry using an adaptable data dictionary.

Results: Clinical laboratory data were extracted from EPIC Clarity across several participating institutions. Labs were transformed, remapped and imported into the MCC registry using the EHR labs abstraction (eLAB) pipeline. Forty-nine clinical tests encompassing 482,450 results were imported into the registry for 1,109 enrolled MCC patients. Data-quality assessment revealed highly accurate, valid labs. Univariate modeling was performed for labs at baseline on overall survival (N=176) using this clinical informatics pipeline.

Conclusion: We demonstrate feasibility of the facile eLAB workflow. EHR data is successfully transformed, and bulk-loaded/imported into a REDCap-based national registry to execute real-world data analysis and interoperability. We provide the source code (github.com/TheMillerLab/eLAB) to the research community for implementation into clinical research pipelines.

Poster Number 51

Carina Shiau, BA
Radiation Oncology, Clinical Research Coordinator | cshiau@mgh.harvard.edu

Dissecting multicellular neighborhoods of pancreatic cancer using spatial molecular imaging at a single-cell resolution

INVESTIGATORS: C. Shiau, J. Su, J. A. Guo, M. Gregory, Y. Kim, S. Kim, J. Reeves, T. Jacks, D. Ting, W. L. Hwang

Pancreatic ductal adenocarcinoma (PDAC) is projected to be the second leading cause of cancer mortality in the United States by 2030. Given that resistance to cytotoxic therapy is pervasive, it is critical to elucidate gene expression programs and spatial relationships among malignant and stromal cells in the tumor microenvironment. We previously discovered expression programs across malignant cells and fibroblasts that formed the basis for a refined molecular taxonomy when we developed and applied a single-nucleus RNA-seq (snRNA-seq) technique to 43 banked frozen primary PDAC specimens that either received neoadjuvant therapy (n=25) or were treatment-naïve (n=18). We also identified three multicellular neighborhoods (annotated as classical, squamoid-basaloid, and treatment-enriched) when we performed whole-transcriptome digital spatial profiling (DSP) using the Nanostring GeoMx platform on 21 formalin-fixed paraffin-embedded sections.

To dissect the multicellular intra-tumoral organization with greater precision, we mapped our malignant/fibroblast programs and immune subsets at a single-cell spatial resolution by performing spatial molecular imaging (SMI) on the Nanostring CosMx platform (pre-commercial). We used a kiloplex (960 target) RNA panel to profile 7 tumors that were treatment-naïve (n=2), received chemo-radiation (CRT; n=4), or received chemo-radiation and losartan (CRTL; n=1). Spatially resolved single-cell data enabled us to explore treatment-associated remodeling of cell type distributions, glandular heterogeneity of malignant programs, and receptor-ligand interactions at an unprecedented resolution. Overall, we demonstrate the tremendous utility of leveraging the first-of-its-kind matched complementary datasets from snRNA-seq, whole-transcriptome DSP, and kiloplex SMI to develop a high-resolution molecular framework that can be harnessed to augment precision oncology efforts in pancreatic cancer.

Poster Number 52

Praveer Singh, PhD
Radiology, Research Fellow | psingh19@mgh.harvard.edu

Can the eye be a window to the lungs? AI predicts Bronchopulmonary Dysplasia through Retinal Fundus Photographs

INVESTIGATORS: J. KALPATHY-CRAMER, iROP

Bronchopulmonary Dysplasia (BPD) is the leading cause of serious pulmonary morbidity in premature infants. Recent work has found that retinal fundus photos (RFPs) can contain information relevant to systemic health in adults. In this study, we evaluated the hypothesis that RFPs obtained as part of ROP screening may predict a future diagnosis of BPD.

As part of a multi-institutional i-ROP study, 1284 RFPs were collected from 477 patients, filtering out all those either without a diagnosis of BPD or captured at PMA>=34 weeks (since BPD is diagnosed at 36 weeks PMA). A Deep Learning (DL) model was trained to predict BPD at 36 weeks using TrainSet. The best performing model with the highest AUC-ROC score on ValSet was finally evaluated on TestSet. To avoid the DL model learning any common biomarkers with ROP disease, a secondary model was trained with only Non-ROP images using a pruned TrainSet, though the performance was reported on the original TestSet.

The model trained with the original TrainSet performs with an overall AUC-ROC of 0.86 on the TestSet. Performance improves to 0.87 when the model is trained on the pruned TrainSet.

We found that a DL model trained on RFPs could predict a future diagnosis of BPD, even in babies with no clinical signs of ROP. In other words, the model isn't just learning that BPD and ROP often occur in the same babies. Early identification of babies at high risk for BPD may facilitate interventional trials to reduce morbidity from BPD in the future.

Computational, Bioinformatics & AI

Poster Number 53

Sonu Subudhi, MBBS, PhD
Radiation Oncology, Research Fellow | ssubudhi@mgh.harvard.edu

Strategies to minimize heterogeneity and optimize clinical trials in Acute Respiratory Distress Syndrome (ARDS): Insights from mathematical modelling

INVESTIGATORS: S. Subudhi, C. Voutouri, C. C. Hardin, M. R. Nikmaneshi, A. B. Patel, A. Verma, M. J. Khandekar, S. Dutta, T. Stylianopoulos, R. K. Jain, L. L. Munn

Background: Mathematical modelling may aid in understanding the complex interactions between injury and immune response in critical illness.

Methods: We utilize a system biology model of COVID-19 to analyze the effect of altering baseline patient characteristics on the outcome of immunomodulatory therapies. We create example parameter sets meant to mimic diverse patient types. For each patient type, we define the optimal treatment, identify biologic programs responsible for clinical responses, and predict biomarkers of those programs.
Findings: Model states representing older and hyperinflamed patients respond better to immunomodulation than those representing obese and diabetic patients. The disparate clinical responses are driven by distinct biologic programs. Optimal treatment initiation time is determined by neutrophil recruitment, systemic cytokine expression, systemic microthrombosis and the renin-angiotensin system (RAS) in older patients, and by RAS, systemic microthrombosis and trans IL6 signalling for hyperinflamed patients. For older and hyperinflamed patients, IL6 modulating therapy is predicted to be optimal when initiated very early (<4th day of infection) and broad immunosuppression therapy (corticosteroids) is predicted to be optimally initiated later in the disease (7th – 9th day of infection). We show that markers of biologic programs identified by the model correspond to clinically identified markers of disease severity.

Interpretation: We demonstrate that modelling of COVID-19 pathobiology can suggest biomarkers that predict optimal response to a given immunomodulatory treatment. Use of the model may help physicians tailor treatments to different patients and also indicate which patients are most likely to respond to certain drugs tested in clinical trials.

Poster Number 54

Augustine Bannerman, BA
Ophthalmology, Research Technician | augustine_bannerman@meei.harvard.edu

Creating a Mentorship, Research, and Virtual Shadowing Program for Underrepresented Minority Undergraduates During COVID-19

INVESTIGATORS: A. Bannerman, E. S. Lu, D. A. Bryant, J. B. Miller

Purpose: To offer early ophthalmology exposure to underrepresented minority (URM) premedical undergraduate students through clinical, research, and mentorship opportunities in an effort to increase URM trainees in the ophthalmology pipeline.

Methods: An ophthalmology mentorship program for URM undergraduate students was launched in the spring 2021 semester and continued through the fall 2021 semester. The program offered clinical experience through virtual shadowing sessions, research opportunities, and mentorship for applying to medical school and supporting career development. Twenty-two undergraduate students (including 13 returning students from the first session) were paired with 13 mentors composed of medical students, residents, and post-doctoral fellows. As part of the Virtual Shadowing Series, 8 ophthalmology faculty hosted 1-hour sessions during which they presented patient cases and surgical videos and shared their career paths.

Results: In a survey, respondents reported increased interest in ophthalmology (16/18, 89%), medicine (15/18, 83%), and research (12/18, 67%). Students attended an average of 3.72 (median 3.5) of the 8 virtual shadowing sessions offered. All respondents met with their mentor or attended a virtual shadowing session at least once, and all respondents indicated an interest in continuing to participate in the program. In addition to virtual shadowing, 3 students shadowed in the operating room for a half-day, observing vitreoretinal surgery through a heads-up 3D surgery platform.

Conclusions: A program offering mentorship, research opportunities, and virtual shadowing experiences for URM undergraduate students increased interest in ophthalmology, medicine, and research for the majority of the students, and may serve as a model for other institutions.

Poster Number 55

Bianca Biglione, BS
Dermatology, Clinical Research Fellow | bbiglione@mgh.harvard.edu

Drug reaction with eosinophilia and systemic symptoms (DRESS) in patients hospitalized with COVID-19: A case series from a large US healthcare system

INVESTIGATORS: B. Biglione, B. Cucka, L. Zhou, E. J. Phillips, F. Bassir, U. Samarakoon, R. Rrapi, S. Chand, L. Wang, S. Alvarez-Arango, K. G. Blumenthal, D. Kroshinsky

Background: Patients hospitalized with coronavirus disease 2019 (COVID-19) often have complicated courses with exposure to drugs associated with drug reaction with eosinophilia and systemic symptoms (DRESS). DRESS is a drug-induced systemic hypersensitivity reaction that classically presents with a rash, fever, hematological abnormalities (eosinophilia, atypical lymphocytosis), and internal organ involvement.

Methods: A retrospective chart review of 9,330 COVID-19 PCR positive patients and 144 DRESS cases between 1/20/20-5/20/21 was performed. Patients with DRESS syndrome occurring concurrently with COVID-19 were assessed for clinical characteristics, culprit drugs, treatments, and outcomes by both a board-certified dermatologist and allergist/immunologist.

Results: Among 6 confirmed cases of concurrent DRESS and COVID-19(incidence 6.43 per 10,000 inpatients with SARS-CoV-2), all patients were critically ill, requiring intensive care unit admission and endotracheal intubation. Patients received vancomycin(100%), cefepime(83%), corticosteroids(67%), remdesivir(50%), azithromycin(50%), hydroxychloroquine(50%), tocilizumab(50%), and meropenem(50%). The culprit drugs for DRESS syndrome were vancomycin, cefepime, and meropenem with no cases due to drugs utilized for the treatment of COVID-19. The mean absolute eosinophil count(AEC) was 4471±1054 K/L(range 2970-5830 K/L). Cases had multi-organ involvement of the kidney(100%) and liver(83%). 5(83%) received systemic steroids for a mean of 24 days. All cases survived to discharge.

Conclusion: DRESS syndrome can occur in the setting of SARS-CoV-2 infection, particularly from antibiotics in patients with longer length of stay. Cases had high eosinophil counts but all survived to discharge. All cases of DRESS were antibiotic-related, therefore, measures to avoid unnecessary antibiotics may help prevent the development of severe adverse drug reactions.

Poster Number 56

Evelynne Fulda, BA
Medicine, Senior Clinical Research Coordinator| efulda@mgh.harvard.edu

COVID-19 Vaccination Rates in a Global HIV Cohort

INVESTIGATORS: E. S. Fulda, K. V. Fitch, E. T. Overton, M. V. Zanni, J. A. Aberg, J. S. Currier, M. T. Lu, C. Malvestutto, C. J. Fichtenbaum, E. Martinez, T. Umbleja, P. S. Douglas, H. J. Ribaudo, S. K. Grinspoon, The REPRIEVE Trial

Little is known regarding global COVID-19 vaccination rates in people living with HIV (PWH), an immunocompromised, vulnerable population with significant morbidity from COVID-19. The Randomized Trial to Prevent Vascular Events (REPRIEVE) is a primary cardiovascular prevention trial among PWH (N=7770) with representation from >100 sites across twelve countries (Brazil, Botswana, Canada, Haiti, India, Peru, Spain, South Africa, Thailand, Uganda, United States, Zimbabwe).

We assessed cumulative COVID-19 vaccination rates from December 2020 through December 2021 among active participants and compared rates to region- and country-specific vaccination data among the general population, determined from publicly available datasets. Secondarily, within the REPRIEVE cohort, demographic, cardiovascular, and HIV-specific data were compared among those vaccinated vs not via Kaplan-Meier estimation.

The cumulative probability of COVID-19 vaccination through the end of December 2021 was 74% among REPRIEVE participants, with rates varying substantially by global burden of disease (GBD) super-region and specific countries. Cumulative vaccination rates were highest in the Southeast/East Asia super-region (93%), followed by High-Income (78%), South Asia (78%), Latin America and the Caribbean (71%), and Sub-Saharan Africa (48%). Country-specific rates varied dramatically, with vaccination rates highest in Thailand (93%) and lowest in Haiti (0%). Overall factors associated with COVID-19 vaccination among PWH included older age, White race, natal male sex, higher BMI, and longer duration of ART use. Vaccination rates among PWH in REPRIEVE were largely comparable to the general population.

Poster Number 57

Yodeline Guillaume, MA
Medicine, Senior Research Technologist | yguillaume@mgh.harvard.edu

Disparities in SARS-CoV-2 seropositivity: evidence from a citywide seroprevalence study in Holyoke, Massachusetts, USA

INVESTIGATORS: W. R. Matias, I. R. Fulcher, S. M. Sauer, C. P. Nolan, Y. Guillaume, J. Zhu, F. J. Molano, E. Uceta, S. Collins, D. M. Slater, V. M. Sanchez, S. Moheed, J. B. Harris, R. C. Charles, R. M. Paxton, S. F. Gonsalves, M. F. Franke, L. C. Ivers

Routine testing often underestimates the true prevalence of SARS-CoV-2 infections. Seroprevalence studies can do this more accurately and provide key information for identifying hotspots, high-risk groups and informing local public health responses. We conducted a city-level seroprevalence study in Holyoke, Massachusetts, USA to estimate the seroprevalence and risk factors for SARS-CoV-2 antibodies. We invited 2,000 randomly sampled households between 11/5/2020 – 12/31/2020 to complete questionnaires and provide dried blood spots for SARS-CoV-2 antibody testing. The study showed that SARS-CoV-2 IgG antibody seroprevalence in Holyoke was only 13.1% during the second surge, far from accepted thresholds for "herd immunity." People identifying as Hispanic, from Spanish-speaking households, and those living in high vulnerability areas were at high risk of prior infection, in-line with known SARS-CoV-2 disparities. These disparities in SARS-CoV-2 exposure require proactive public health interventions to support high-risk groups.

Poster Number 58

Nikolaus Jilg, MD, PhD
Medicine, Clinical Research Fellow | njilg@partners.org

Camostat is not Effective for Mild-to-Moderate COVID-19 in a Phase 2 Trial of ACTIV-2

INVESTIGATORS: N. Jilg, K. W. Chew, M. Giganti, E. Daar, D. Wohl, A. C. Javan, A. Kantor, P. Hart, J. Eron, J. Currier, M. Hughes, D. Smith, J. Z. Li, ACTIV-2/A5401 Study Team

Background/Rationale: Globally accessible therapies for COVID-19 are a high priority. Camostat, an affordable and safe oral medication, efficiently blocks SARS-CoV-2 infection in vitro. ACTIV-2/A5401 is a platform trial evaluating safety and efficacy of therapies in symptomatic outpatients with mild-moderate COVID-19.

Methods: In a phase 2 sub-study of ACTIV-2/A5401, participants were randomized to camostat 200mg orally four times per day for 7 days or placebo. Objectives were safety and efficacy of camostat to reduce COVID-19 symptoms and increase the proportion of participants with SARS-CoV-2 RNA below the lower limit of quantification from nasopharyngeal swabs on days 3, 7, and 14.

Results: Two-hundred fifteen individuals (108 camostat, 107 placebo) initiated study intervention. Fifty-four percent were female, >99% cis-gender, 9% Black, and 51% Latinx. Median age was 37 years; 47% reported ≤5 days of symptoms, 26% met the protocol definition of higher risk of progression to severe COVID-19. Frequent symptoms were cough (86%), fatigue (85%), nasal obstruction/congestion (71%) and body/muscle aches (71%). Adverse events were similar and median time to improvement was 9 days for both groups. Proportions of participants with positive SARS-CoV-2 RNA did not differ significantly between camostat and placebo, on day 3 (31% vs. 40%), 7 (64% vs. 68%), and 14 (87% vs. 88%). Eleven participants, 6 (5.6%) in the camostat and 5 (4.7%) in the placebo group, were hospitalized through day 28.

Conclusions: Here we show that camostat was well tolerated but demonstrated no antiviral or clinical efficacy. This highlights the critical importance of randomized controlled trials.

Poster Number 59

Caitlin Marino, BS
Ragon Institute, Research Technician | cmarino5@mgh.harvard.edu

Transmissibility of SARS-CoV-2 variants of concern, Delta and Omicron: virologic features of infection and antigen testing

INVESTIGATORS: C. T. Marino, J. Boucau, J. Z. Li, J. E. Lemieux, M. J. Siedner, A. K. Barczak, On behalf of the POSITIVES consortium

Since SARS-CoV-2 was introduce into the Massachusetts population in March 2020, there have been 21,546 confirmed deaths. Multiple variants of concern have arisen from the original SARS-CoV-2 strain; the most recent being the delta and the omicron variants, with current estimates of confirmed fatalities 1400 and 2700, respectively. Although several public health initiatives (i.e., masking, vaccines, antigen testing, and isolation recommendations) have been implemented to reduce SARS-CoV-2 transmission and disease severity, variant-specific data relevant to these guidelines is just emerging. We enrolled symptomatic vaccinated and unvaccinated individuals newly diagnosed with COVID-19 in a longitudinal study. Serial nasal swabs were performed and analyzed by sequencing and culture. A subset of swabs was subjected to antigen testing. Despite differences in clinical features of infection, virologic features were indistinguishable, with similar time to culture conversion. Five days after symptom onset or initial positive PCR, 27/36 individuals with delta variant infection and 14/20 individuals with omicron variant infection remained culture positive. In the first 5 days post-infection, lab-based antigen testing was discordant from culture positivity. After day 5, we were not able to culture delta or omicron samples if the antigen test was negative. Time to culture conversion was not different based on vaccine status. Our results demonstrate that individuals with symptomatic disease can shed viable virus for more than 5 days independent of vaccine status, raising the question of whether additional strategies for mitigating risk of ongoing transmission would be of public health benefit.

Poster Number 60

Dylan Rice, BA
Neurology, Clinical Research Coordinator | drice2@mgh.harvard.edu

COVID-19 vaccine acceptance and hesitancy in Chad: A cross-sectional study of patients, community members, and healthcare workers

INVESTIGATORS: D. R. Rice, A. Balamo, A. R. Thierry, A. Gueral, D. Fidele, F. J. Mateen, F. Sakadi

Introduction: As of December 2021, the COVID-19 vaccination rate in Chad approximates 1%. Vaccine hesitancy may negatively impact vaccine uptake; however, there have been no reports of COVID-19 vaccine hesitancy in Chad.

Methods: A prospective convenience cohort of adult patients, community members, and healthcare workers from N'Djamena, Chad (recruited from August to October 2021) completed a 25-question survey instrument exploring demographic, social, and clinical variables related to COVID-19 and an adapted WHO Vaccine Hesitancy Survey. Primary outcomes were vaccine acceptance and vaccine hesitancy. Regression models assessed associations between Vaccine Hesitancy Scale (VHS) scores and pre-selected variables of interest. A qualitative vaccine hesitancy measure was analyzed with inductive thematic analysis.

Results: In 508 participants (32% female; mean age 32 years; 162 patients, 153 community members, 193 healthcare workers), vaccine acceptance approximated 52%. The vaccine concerns most frequently endorsed were: side effects (48%), efficacy (38%), safety (34%), concerns about the pharmaceutical industry (27%), and lack of government trust (21%). Four main themes arose in qualitative responses (n=116): education, trust, clinical concerns, and misinformation and false beliefs.

Over a third of participants were classified as highly COVID-19 vaccine hesitant. Knowing someone who died from COVID-19, believing local healthcare workers support vaccination, trusting the government, having a higher socioeconomic status, and having medical comorbidities were associated with less vaccine hesitancy (all $p<.05$).

Poster Number 61

Isadora Tadeval Lape, BS
Surgery, Research Technician| itadevallape@mgh.harvard.edu

Urinary CRISPR-cas13 assay to monitor rejection in kidney transplant recipients after SARS-CoV-2 mRNA vaccination

INVESTIGATORS: I. Tadeval Lape, A. Al Jurdi, R. Benedetti Gassen, T. J. Borges, F. Hullekes, L. Morena, L. V. Riella

Introduction:
Coronavirus disease (COVID19) is associated with higher mortality in kidney transplant recipients (KTRs). Concerns about the use of mRNA vaccines in KTRs include their excessive activation of the immune system and their potential for triggering allograft rejection. The aim of this study was to monitor KTRs for allograft rejection after mRNA vaccination. Since serum creatinine and proteinuria are not sensitive enough to exclude allograft rejection, we monitored for rejection using a novel CRISPR-Cas13 assay that measures urinary CXCL9 mRNA levels.

Methods:
Urine samples were collected before vaccination (baseline) and one month after the second vaccine dose (month 2) from 26 KTRs. A CRISPR-Cas13 assay developed by our lab was used to detect the urinary biomarker CXCL9 mRNA. We also measured serum creatinine and urine protein-to-creatinine ratio (UPCR) as additional markers of allograft dysfunction.

Results:
Urinary CXCL9 mRNA levels were highly positive at month 2 for only one patient who developed biopsy-proven acute cellular rejection 40 days following initial vaccination. This patient had an elevation in serum creatinine but no change in UPCR. CXCL9 mRNA levels markedly decreased after rejection treatment. The remaining patients had stable creatinine (median 1.17 mg/dL, IQR 0.97-1.54 mg/dL), UPCR (median 0.15 g/g, IQR 0.09-0.27g/g), and low CXCL9 mRNA levels (<100 RFUs). No other patients developed rejection.

Conclusion:
SARS-CoV-2 mRNA vaccination in KTRs was safe and not associated with a significant alloimmune risk of allograft rejection. Our assay is a promising tool to detect urinary CXCL9 mRNA levels as a rejection marker in KTRs.

Poster Number 62

Chrysovalantis Voutouri, PhD
Radiation Oncology, Research Fellow | cvoutouri@mgh.harvard.edu

Requirement for booster doses in healthy, cancer and immunosuppressed patients infected with the ancestral or variant SARS-CoV-2

INVESTIGATORS: C. Voutouri, C. C. Hardin, V. Naranbhai, M. Nikmaneshi, M. J. Khandekar, J. F. Gainor, T. Stylianopoulos, L. L. Munn, R. K. Jain

Current SARS-CoV-2 vaccines are effective at preventing COVID-19 or limiting disease severity in healthy individuals, but effectiveness is lower among patients with cancer or immunosuppression. Vaccine effectiveness wanes with time and varies by vaccine type. Moreover, current vaccines are based on the ancestral SARS-CoV-2 spike protein sequence, and emerging viral variants may evade vaccine induced immunity. Here we describe a mechanistic mathematical model for vaccination-induced immunity and use it to predict vaccine effectiveness, taking into account current and future viral variants and vaccines. We predict the impact on vaccine effectiveness of variants that escape vaccine-induced immunity, are more virulent or more transmissible and in patients with impaired vaccine responses, such as those with concurrent cancer or immunosuppression. The model was validated with available clinical data. Consistent with clinical data the model predicts immunogenicity is enhanced following booster vaccination in patients on immunosuppressive therapies. However, our model predicts that booster doses will be required for these individuals to maintain protective immunity. The model further predicts the impact of potential SARS-CoV2 variants on immunosuppressed individual and predicts the risk of breakthrough infections after a single booster dose. Our modelling is thus useful for anticipating and planning for future vaccination needs, and tailoring strategies to key risk groups.

Poster Number 63

Victoria Chen
Medicine, Undergraduate Student | vjc11@mgh.harvard.edu

Algorithmic Identification of Atypical Diabetes in Electronic Health Record (EHR) Systems

INVESTIGATORS: V. Chen, S. J. Cromer, C. Han, W. Marshall, S. Emongo, T. Majarian, J. C. Florez, J. Mercader, M. Udler

Aims: Understanding atypical forms of diabetes may advance personalized treatment regimens and discovery of novel pathophysiologic mechanisms, but methods to identify patients with atypical diabetes are needed.

Methods: Patients with likely type 2 diabetes (T2D) were identified using a validated machine-learning (ML) algorithm in electronic health record (EHR) data. "Typical" T2D was filtered out through a "base algorithm" excluding individuals with obesity or evidence of dyslipidemia. To filter out type 1 diabetes (T1D), we tested six additional "branch algorithms," relying on clinical characteristics, including autoantibodies, medications, and ML algorithms, resulting in six overlapping cohorts. Diabetes type was classified by manual chart review as atypical, not atypical, or indeterminate due to missing information.

Results: The base and six branch algorithms identified 119 potentially atypical cases, of whom 16 individuals were confirmed to have atypical diabetes after expert review. The branch algorithm excluding T1D by removing patients who had ever used outpatient insulin had the highest percentage yield (13 of 27; 48.2%) of atypical diabetes. The 16 atypical cases had significantly lower BMI and higher HDL compared to an unselected group of individuals with T1D or T2D diagnosis by ML algorithm. Compared to the ML T1D group, the atypical group had a significantly higher T2D polygenic score ($p<0.01$) and lower hemoglobin A1c ($p<0.01$).

Conclusion: EHR-based algorithms to identify individuals with atypical diabetes achieved up to 48% yield. Identifying patients with atypical diabetes may inform the heterogeneity of T2D and identify candidates for studies like the Rare and Atypical Diabetes Network (RADIANT).

Poster Number 64

Caitlin Colling, MD
Medicine, Clinical Research Fellow | ccolling@partners.org

Serum Free Cortisol and Free Cortisol-to-Cortisone Ratio Increase After 10 Days of Overfeeding and After 10 Days of Fasting

INVESTIGATORS: C. Colling, M. Bredella, P. Fazeli, G. Pachon-Pena, R. Singh, C. Rosen, K. Miller

Objective: Chronic caloric deprivation and obesity are complicated by hypercortisolemia. The effects of acute overfeeding and fasting on circulating free cortisol levels and conversion of cortisone to free cortisol are unknown. We hypothesized that serum free cortisol and free cortisol-to-cortisone ratio (a surrogate measure of 11β-hydroxysteroid dehydrogenase [11β-HSD] activity) would increase after both overfeeding and fasting.

Design: Prospective

Methods: 22 healthy volunteers completed a 10-day high-calorie protocol followed by a 10-day fast, separated by a 2-week wash-out. Morning free and total cortisol and free cortisone levels (LC/MS) and percent body fat (DXA) were performed at baseline and after 10 days of each intervention

Results: Both high-calorie feeding and fasting increased total and free cortisol and the free cortisol-to-free cortisone ratio ($p=0.001$ to $p=0.046$). There were sex interactions, with significant effects in men ($p<0.001$), but not women ($p=0.898$ and 1.000, respectively) in subset analyses examining the effects of fasting on free cortisol and the free-to-total cortisol ratio. Baseline percent body fat was inversely associated with change in free cortisol ($p=-0.52$, $p=0.013$) and free cortisol-to-total cortisol ratio ($p=-0.49$, $p=0.021$) during fasting.

Conclusion: Overfeeding and fasting both increase circulating free cortisol levels and appear to alter 1β-HSD activity. Fat mass may be relatively protective against starvation-induced hypercortisolemia in women. Further study is warranted to determine whether elevated cortisol levels contribute to complications of starvation and obesity, such as bone fragility.

Poster Number 65

Snimarjot Kaur, MBBS
Medicine, Clinical Research Fellow | skaur@mgh.harvard.edu

Trajectory of Gonadal Hormones in Adolescent Males Two Years after Sleeve Gastrectomy

INVESTIGATORS: S. Kaur, M. A. Bredella, M. Misra, V. Singhal

Severe obesity is associated with hypogonadism in adolescent and young adult males. Sleeve gastrectomy (SG) is currently the most potent strategy for inducing weight loss. We aimed to determine the impact of SG on Leydig and Sertoli cell function over a period of 24 months, and determinants of these changes.

16 males (SG-6; Non-surgical (NS)controls-10) 13-22 years of age with severe obesity were followed for two years. Participants had blood tests for hormone levels at baseline (BL), 12-month and 24-month visits. Body composition was measured using DXA. SG and NS groups were similar for age and BMI z-scores at BL. There was no difference in testosterone, sex hormone binding globulin (SHBG), estradiol, estrone, anti-mullerian hormone (AMH–Sertoli cell marker) and insulin-like peptide 3(INSL-3-Leydig cell marker) between the two groups at BL. Over 24-months, in SG vs. NS, total testosterone increased (232.7±44.71 vs 34.9±27.71 ng/dL; p=0.005), and SHBG increased (6.5±2.24 vs -3.1±2.41nmol/lt; p= 0.01). Changes in AMH and INSL-3 did not differ between groups. At 12 months, there was an increase in INSL-3 in the SG group(p=0.047) but AMH did not change.

At 12 months, change in INSL-3 was negatively associated with change in BMI (p=-0.79, p=0.02). Change in total testosterone at 12 months was negatively associated with a change in BMI (p=-0.77, p=0.0012), and change in visceral fat (p=-0.68, p= 0.02), and at 24-months with change in BMI (p=-0.55, p=0.05) and percent fat mass (p=-0.65, p=0.02). Leydig cell function improves after 1 year and is stable 2 years after SG and is associated with degree of weight loss. Sertoli cell function remains unchanged after SG.

Poster Number 66

Supritha Nimmala, MBBS
Medicine, Research Fellow | snimmala@mgh.harvard.edu

Relative effectiveness of phentermine with and without topiramate for weight loss in adolescents and young adults with obesity

INVESTIGATORS: S. Nimmala, M. Misra, V. Singhal

The rising prevalence of moderate-severe obesity in adolescents has led to greater use of anti-obesity medications. Phentermine, a sympathomimetic, and topiramate, a GABA agonist, decrease appetite and increase satiety. The combination is approved by the FDA for use in adults for obesity. Data regarding the effectiveness of phentermine with/without topiramate in weight reduction during adolescence are lacking. To examine the effectiveness of prescription phentermine as monotherapy and in combination with prescription topiramate for weight reduction in adolescents with obesity. Chart review of 111 adolescents between 11-21 years with moderate to severe obesity treated at a tertiary center. PHEN group(n=70) was prescribed only phentermine and PHEN/TOP group(n=41) was prescribed phentermine in combination with topiramate. Weight, height, heart rate and blood pressure collected at baseline (medication start), 3, 6 and 12 months. Anthropometric variables calculated using standardized formulae. Mean age in PHEN and PHEN/TOP (18.66 ± 0.26 vs.19.29 ± 0.26) and female/male ratio (53/17 vs. 34/7) was similar. Both groups saw a progressive decrease in weight, body mass index (BMI), BMI Z-score, and BMI percentile from baseline to 12months. PHEN had a baseline median BMI percent of 95th percentile of 136% (122.5, 150.25) and decreased by 8 %; 12 % and 18.5% at 3, 6 and 12 months (all p<0.001). PHEN/TOP had a baseline median BMI percent of 95th percentile of 135 % (122, 151) and decreased by 7 % (p <0.0001), 12 % (p <0.0001) and 16 % (p=0.016) at 3, 6 and 12 months. Similar weight loss was seen when phentermine was prescribed with or without topiramate in adolescents.

Poster Number 67

Jonanlis Ramirez Alcantara, MD
Pediatrics, Clinical Research Fellow | jramirezalcantara@mgh.harvard.edu

Adrenal Insufficiency in Pediatric Patients with Adrenoleukodystrophy in the Era of the Newborn Screening

INVESTIGATORS: J. Ramirez Alcantara, N. Grant, T. Stanley, F. Eichler, A. Halper

OBJECTIVE
We set out to investigate whether the diagnosis of Adrenoleukodystrophy (ALD) by newborn screening (NBS) has altered the time to diagnosis of adrenal insufficiency (AI) in children with ALD.

METHODS
We conducted a retrospective medical chart review of all children with ALD seen between May 2006 through June 2021 at MGH. We determined how many patients were diagnosed with ALD by NBS and outside the newborn period. Separately, we determined the age of AI diagnosis. We subclassified AI as latent or symptomatic.

RESULTS
We included 74 patients with ALD (69[93%] male, 5[7%] female). Patients ranged from 2.4 months to 17.8 years of age. Twenty-two (30%) patients were diagnosed with ALD by NBS.
We identified 52(70%) patients (all male) with AI. Of these patients, 9(17%) were diagnosed with ALD by NBS. Of the nine patients diagnosed by NBS, 6(66%) had latent AI, and 3(33%) had symptomatic AI. Of the remaining 43 patients, 17(40%) had latent AI, 23(53%) had symptomatic AI, and 3(7%) patients had insufficient information.
Patients diagnosed with ALD by NBS had significantly earlier AI diagnosis than patients diagnosed outside the newborn period (mean age at diagnosis 0.79 ± 0.77 years for those diagnosed by NBS vs. 5.6 ± 3.5 years, $p<0.0001$).

CONCLUSION
Our results suggest that ALD implementation as part of the NBS leads to significantly earlier AI detection and initiation of glucocorticoid treatment. Considering these findings, the diagnosis of ALD by NBS should improve care and clinical outcomes for patients with ALD and AI across the United States.

Poster Number 68

Grace Shen, BS
Medicine, Clinical Research Coordinator | gshen3@mgh.harvard.edu

Role of Renin-Angiotensin-Aldosterone Activation in Arterial Inflammation in HIV

INVESTIGATORS: G. Shen, T. S. Thomas, A. R. Walpert, K. V. Fitch, C. DeFelippi, G. K. Adler, S. K. Grinspoon, S. Srinivasa

Arterial inflammation remains increased among persons with HIV(PWH) compared to persons without HIV(PWOH) and may contribute to atherosclerotic disease. We previously demonstrated unique renin-angiotensin-aldosterone-system (RAAS) physiology among PWH and here investigate whether increased RAAS activation contributes to arterial inflammation in HIV.

20 PWH and 9 PWOH followed controlled sodium diets to simulate RAAS activation and suppression. We measured serum lipoprotein-associated phospholipase-A2(LpPLA2), a marker of arterial inflammation, following both conditions to assess the physiologic dynamics of aldosterone in relation to arterial inflammation.

PWH (age 48.9±1.5 years, male sex 65%) were of similar age and sex to PWOH (age 51.4±2.4 years, male sex 67%), demonstrated good immunologic control (CD4+ count 571.5±72.6 cells/mL, log HIV viral load 1.8±0.2 copies/mL), and had long histories of HIV infection (18.4±1.5 years) and antiretroviral medication use (10.9±1.2 years). Both groups were of similar overweight BMI. Aldosterone was significantly higher in PWH than PWOH during RAAS activation (13.8[9.7, 30.9] vs. 9.1[7.4, 12.8] ng/dL, P=0.02). LpPLA2 was significantly higher in PWH than PWOH during both RAAS activation (237.3[190.1, 276.5] vs. 179.9[132.8, 214.8]ng/mL, P=0.01) and suppression (196.5[173.3, 240.1] vs. 171.5[151.6, 183.8]ng/mL, P=0.01). Among PWH only, LpPLA2 increased significantly with RAAS activation (P =0.03). During RAAS activation, LpPLA2 was significantly related to aldosterone (r=0.39, P=0.04) among all participants and to visceral fat (r=0.46, P=0.04) and systolic blood pressure (r=0.57, P=0.01) among PWH only.

Increased LpPLA2 in HIV during RAAS activation suggests a potential association between aldosterone and arterial inflammation. These data may inform future studies that test RAAS blockade as a targeted treatment for cardiovascular disease in HIV.

Poster Number 69

Takahiro Shimizu, MD
Surgery, Research Fellow | TSHIMIZU2@mgh.harvard.edu

Müllerian inhibiting substance type 2 receptor (MISR2) function in the human adrenal

INVESTIGATORS: D. Pepin, R. A. Hodin, P. K. Donahoe

Müllerian inhibiting substance (MIS), a member of the transforming growth factor beta family, is known to regulate the development and function of reproductive organs in a receptor mediated fashion via its type 2 receptor, MISR2. The expression of MISR2 was recently detected in human adrenal; however, its function remains unknown. [Methods] After approval by the local ethical committee and informed consent, adrenal surgical specimens were banked, RNA extracted, and primary cell cultures established. Primary adrenocortical adenoma cell lines and the adrenocortical carcinoma cell line(H295r) were then treated with recombinant human MIS (rhMIS) and/or BMP-2 and followed at various intervals to characterize downstream signaling. [Results] Quantitative PCR analyses and in-situ hybridization with RNA scope detected MISR2 expression in human 1) normal adrenal glands, 2) adrenocortical hyperplasia, 3) adrenocortical adenomas, and in the human adrenocortical carcinoma cell line(H295r); adrenal expression was found to be higher than that of human granulosa cells. Furthermore, MISR2 was localized throughout the adrenal cortex. Western blot showed in primary cells from adrenocortical adenomas that, while BMP-2 activated the canonical SMAD 1/5/8 pathway, recombinant human MIS (rhMIS) activated noncanonical pathway through AKT and STAT3 phosphorylation. Both BMP-2 and rhMIS activated ERK phosphorylation. In the human adrenocortical carcinoma cell line(H295r), CYP11A1 and CYP17A were downregulated in a time series after 4 hours of treatment with both rhMIS and BMP-2. [Conclusion] MIS appears to regulate steroid biosynthesis adrenal carcinoma cells but not in adrenocortical adenomas. Furthermore, MIS may signal primarily through noncanonical pathways in adrenocortical adenomas.

Poster Number 70

Maria Stamou, MD, PhD
Medicine, Clinical Research Fellow | jmstamou@mgh.harvard.edu

De novo Copy Number Variant Analysis in Idiopathic Hypogonadotropic Hypogonadism (IHH) implicates EMX2 gene variants in human infertility

INVESTIGATORS: M. I. Stamou, H. Brand, I. Wong, R. Rojas, L. Plummer, M. F. Lippincott, R. Balasubramanian, M. E. Talkowski, S. Seminara

Introduction: Idiopathic Hypogonadotropic Hypogonadism (IHH) is a rare inherited disorder of infertility caused by Gonadotropic Releasing Hormone (GnRH) deficiency. To-date, only ~40% of the genetic etiology of IHH is known. Copy number variants (CNVs) gleaned from karyotypes/microarray data have previously identified IHH genes. Hence, we hypothesized that de novo CNVs in IHH patients will mark novel genes.

Methods: We performed CNV analyses in exome sequencing data from 293 IHH proband-parent trios using the GATK-gCNV algorithm. We prioritized de novo CNVs that disrupted genomic regions containing genetically-constrained haploinsufficient genes. Candidate genes were validated by rare variant association testing (RVAT) for CNVs/single nucleotide variants (SNVs) between the IHH cohort [n=1394] and gnomAD-database [n=113,473]. Gene expression of the candidate genes was examined in RNA-sequencing data from IPSc-derived GnRH cell-lines.

Results: We identified 44 de novo deletions encompassing 334 genes, of which 30 genes were genetically constrained. By applying RVAT, we identified a novel gene, EMX2 (empty spiracles homeobox-2, transcription factor) that was enriched for rare loss-of-function variants in IHH. EMX2 was highly expressed in IPSc GnRH cells, is known to interact with IHH-related proteins (fgf8 and gli3), and transgenic Emx2 mice display reproductive phenotypes. While a proband with a multigenic deletion spanning EMX2 exhibited a complex phenotype (IHH, anosmia, developmental delay, hearing loss and microcephaly), a proband with a EMX2 nonsense SNV displayed IHH and anosmia without other features.

Conclusions: By performing a CNV analysis that prioritized de novo variants, we uncovered EMX2 gene as a novel IHH candidate gene for human infertility.

Poster Number 71

Teressa Sumy Thomas, MBChB
Medicine, Research Fellow |TSTHOMAS@mgh.harvard.edu

Visceral adiposity index as a measure of cardiometabolic disease in persons living with HIV

INVESTIGATORS: T. S. Thomas, S. Iyengar, G. Shen, A. R. Walpert, G. K. Adler, S. K. Grinspoon, S. Srinivasa

Well-treated persons living with HIV (PLWH) are predisposed to fat redistribution and accumulation of visceral adipose tissue (VAT), a highly inflamed and dysfunctional ectopic fat depot, and demonstrate a 2-fold higher risk of cardiovascular disease (CVD) compared to those without HIV. Gold-standard measures of VAT by CT and MRI are not used clinically. The visceral-adiposity-index (VAI) is a tool combining biochemical measures (triglycerides, HDL) with anthropometrics (waist circumference (WC), BMI) in an easily computed sex-specific formula.

45 PLWH without known CVD were included if they had virological control (HIV viral load<200 copies/mL) and abdominal VAT area>110cm2 on CT. Coronary plaque was measured using coronary CT-angiography or PET scans. Linear regression was performed to assess relationships with VAI. Non-normally distributed variables were log-transformed.

Participants [male(73%), Caucasian(53%), non-Hispanic(84%)], with mean age 55±7 years and long durations of HIV(20±8 years) and ART use[15(12,19) years] were obese (BMI 31.9±5.8 kg/m^2) with VAT 189[127,267]cm^2 and VAI 4.9[2.8,7.3]. VAI correlated strongly with VAT (r=0.59, P<0.0001), anthropometric measures (BMI r=0.36, P=0.02; WC r=0.43, P=0.004; WHR r=0.33, P=0.03) and ALT (r=0.32, P=0.03), and did not relate to HIV-specific and other metabolic parameters (blood pressure, HbA1c). Participants with coronary plaque tended to have a higher VAI compared to those without (log VAI 0.7±0.3 vs. 0.5±0.3, P=0.056).

These data show VAI strongly correlates with abdominal VAT area and may be a useful biomarker for visceral adiposity in HIV. Furthermore, VAI may relate to ALT and coronary plaque, helping identify those PLWH at risk for fatty liver and heart disease, respectively.

Poster Number 72

Hannah Contreras, BA
Surgery, Research Technician | hannah.contreras@mgh.harvard.edu

A mouse model of PLS3-associated congenital anomaly syndrome demonstrates functions in the diaphragm, body wall, and bone

INVESTIGATORS: H. T. Contreras, J. Wells, R. Maser, E. L. Bogenschutz, C. J. Bult, P. K. Donahoe, F. A. High

Congenital diaphragmatic hernia (CDH) is a common, genetically heterogeneous structural birth defect associated with high mortality and morbidity. We described a novel X-linked congenital anomaly syndrome characterized by CDH and anterior body wall defects that is caused by variants in PLS3. This gene encodes an acting bundling protein and is causative of X-linked osteoporosis, a distinct allelic disorder not associated with congenital anomalies. CDH-associated PLS3 variants are all missense, affect the actin binding domains of the protein, and differ from the loss-of-function variants seen in patients with osteoporosis. To model these distinct CDH disorders, we characterized two Pls3 mouse lines: a knock-in variant identified in one of the affected families with CDH (Pls3W499C), and a deletion that results in a frameshift loss-of-function allele (Pls314bddel). Both hemizygous male and homozygous female Pls3W499C knock-in mice demonstrated partial perinatal lethality, while the Pls314bpdel mice were viable and fertile. Pls3W499C mice recapitulated the key findings of the human phenotype, including diaphragm and abdominal wall defects. Body wall defects included omphalocele and widening of the space between the abdominal oblique muscles. We studied bone mineral density in mice at 3 months of age using dual energy x-ray absorptiometry (DEXA). The Pls314bpdel mice demonstrated decreased bone mineral density compared with controls, consistent with loss-of-function of PLS3 as the predominant mechanism in osteoporosis. In contrast, the Pls3W499C mice showed statistically significant increased bone mineral density, supporting gain-of-function in the p.W499C variant in bone. These findings explain the disparate clinical phenotypes seen with different human variants in PLS3.

Poster Number 73

Saurja DasGupta, PhD
Center for Computational and Integrative Biology, Research Fellow | dasgupta@molbio.mgh.harvard.edu

Prebiotic RNA Assembly: Chemistry, Catalysis, and Compartmentalization

INVESTIGATORS: S. DasGupta, T. S. Walton, A. Radakovic, S. J. Zhang, J. W. Szostak

We are building experimental models for the major chemical transitions that produced cellular life from a collection of small molecules. Primitive life would have minimally consisted of genes and enzymes within cell-like compartments. Since RNA functions as genes as well as enzymes and can emerge via prebiotic synthetic pathways, we focused on creating RNA-based life. RNA-based early life must have required pathways for RNA assembly from shorter building blocks, which needed to be chemically activated. RNA assembly without enzymes is inefficient, therefore, the appearance of RNA enzymes or ribozymes that catalyse RNA assembly from prebiotically-activated building blocks must have been critical.

We used laboratory evolution to isolate such ribozymes from combinatorial libraries and showed that these ribozymes can function under the chemical conditions required by prebiotic activation of RNA building blocks. These ribozymes, therefore, connect nonenzymatic and enzymatic assembly of prebiotically-activated RNA building blocks. Further, we demonstrated that ribozymes that catalyse RNA assembly can themselves be assembled from aminoacylated RNAs without enzymes. There ribozymes contain backbones made of amino acid linkages in addition to their native phosphodiester bonds, representing a new hybrid catalytic polymer.

All life is cellular, where enzymes are encapsulated within compartments bounded by amphiphilic molecules. As a first step toward a self-replicating primitive cell, we encapsulated these ribozymes within fatty acid vesicles and established the first instance of RNA-catalyzed RNA assembly inside prebiotic fatty acid compartments. Our efforts to integrate various aspects of RNA assembly have brought us closer to assembling self-replicating cells capable of evolving spontaneously.

Poster Number 74

Cameron Douglas, BA, BS
Center for Genomic Medicine, Research Technician | cjdouglas@mgh.harvard.edu

Implementing an in vivo CRISPR-Cas9 knockout system to identify genetic modifiers of somatic CAG repeat instability in Huntington's Disease.

INVESTIGATORS: C. J. Douglas, A. Azevedo, R. Murtha, J. Ulloa, M. Kovalenko, M. A. Andrew, F. Zhang, V. C. Wheeler, R. M. Pinto, CHDI Foundation

Huntington's disease (HD) is a neurodegenerative disorder caused by a CAG repeat expansion. Further somatic expansion of the CAG repeat occurs in a time-dependent and tissue/cell-type specific manner, and is inversely correlated with age of motor onset in patients. Further, DNA repair genes have been identified as modifiers of HD onset in a GWAS. These data indicate that somatic CAG expansion is a critical disease driver and that therapeutic targeting of this process will slow the disease course.

Here, with the goal of further dissecting the mechanism(s) underlying somatic CAG repeat expansion in brain, we report the development of an in vivo CRISPR/Cas9-based platform to identify novel instability modifiers: using HD KI mice that endogenously express Cas9, and AAV-based delivery with AAV8 and PHP.eB serotypes, we were able to efficiently KO known modifier genes in the liver and brain of adult mice, and successfully suppress or enhance somatic CAG expansions. We have now applied this platform to discover new modifier genes.

Poster Number 75

Ricardo Harripaul, PhD
Neurology, Research Fellow| RHARRIPAUL@MGH.HARVARD.EDU

Neuronal Tissue-Specific Analysis Converges on the Peripheral Nervous System as a Key Driver in Features of Familial Dysautonomia

INVESTIGATORS: R. S. Harripaul, E. Morini, D. Gao, E. M. Logan, E. G. Kirchner, J. Bolduc, A. Chekuri, M. Salani, B. Currall, R. Yadav, S. Erdin, M. E. Talkowski, S. Slaugenhaupt

Familial Dysautonomia (FD) is a rare, recessive neurodegenerative disease that is caused by a splicing mutation in intron 20 of the Elongator complex protein 1 (ELP1, alias IKBKAP). FD is a complex disorder affecting both the sensory and autonomic nervous systems but how different regions of the brain are affected by the variable loss of ELP1 is currently unknown. Here, we report transcriptome analyses across a broad range of brain tissues using phenotypic mice expressing human ELP1 with the FD mutation. We investigated the transcriptome changes in the cortex, dorsal root ganglion (DRG), medulla, spinal cord and trigeminal from 3-month, control and FD mice via a generalized linear model framework, correcting for confounding factors and robustly estimating disease effect. The two tissues from the peripheral nervous system (PNS), trigeminal and DRG, shared 191 differentially expressed genes (DEGs) compared to the other three tissues from the central nervous system. In addition, there was a statistically significant overlap of DEGs in trigeminal and DRG tissues, which indicates a convergent dysregulation in the PNS. More importantly, the shared DEGs in the PNS show enrichment for GO Biological Process terms related to neuronal functions such as "cell-cell signalling"; "regulation of neuron differentiation"; "modulation of chemical synaptic signalling". We intend to dissect these DEGs further with co-expression and interaction networks to demonstrate their functional importance and links to the FD etiology. This study is the first to explore the tissue-specific differences in FD neuronal tissues and provides evidence that the disease preferentially targets PNS tissues.

Poster Number 76

Dimitri Maamari, MD
Center for Genomic Medicine, Clinical Research Fellow | dmaamari@mgh.harvard.edu

Impact of combined monogenic and polygenic risk for coronary artery disease in a Preventive Genomics Clinic – a single-site implementation study

INVESTIGATORS: D. J. Maamari, D. G. Brockman, K. Aragam, R. C. Pelletier, E. Folkerts, C. L. Neben, S. Okumura, L. E. Hull, A. A. Philippakis, P. Natarajan, P. T. Ellinor, K. Ng, A. Y. Zhou, A. V. Khera, A. C. Fahed

State-of-the-art genetic risk interpretation for a common complex disease such as coronary artery disease (CAD) requires assessment for both monogenic variants – such as those related to familial hypercholesterolemia – as well as the cumulative impact of many common variants, as quantified by a polygenic score. Here, we describe our experience returning a clinical test inclusive of both monogenic and polygenic risk for CAD in the Massachusetts General Hospital Preventive Genomics Clinic. Forty-five participants (mean age 51 years, 38% women, 71% with no known CAD) took part in the study, including 25 (56%) referred by their physicians and 20 (45%) self-referred. Two (5%) participants had a monogenic variant pathogenic for familial hypercholesterolemia, and an additional nine (20%) participants had a polygenic score in the top quintile of the population distribution. In a post-disclosure survey completed by 26 participants, both the genetic test report (in 89% of participants) and the discussion with the clinician (in 96% of participants) were ranked as very helpful in understanding the result. Nearly half of participants without CAD (15 out of 31 patients or 48%) had a change in management including statin initiation, statin intensification, or coronary imaging. We provide a generalizable framework for a combined monogenic and polygenic risk disclosure in a clinical setting that could inform future clinical implementation and research.

Poster Number 77

Ernst Mayerhofer, MD
Center for Genomic Medicine, Research Fellow | emayerhofer@mgh.harvard.edu

Genetically predicted on-statin LDL response is associated with higher risk of intracerebral hemorrhage

INVESTIGATORS: E. Mayerhofer, R. Malik, M. Dichgans, J. Rosand, C. D. Anderson, M. K. Georgakis

Background and Aims: It remains unclear whether stain-induced LDL lowering influences risk of intracerebral hemorrhage (ICH). We explored whether genetically predicted LDL response to statins is associated with ICH risk.

Methods: Utilizing genomic data from randomized trials, we derived a 35-SNP score of on-statin LDL response and tested it in the population-based UK-Biobank (UKB). We extracted statin drug and dose data from primary care data on a subset of UKB participants covering a period of 29 years (225,195 individuals). We validated the effects of the genetic score on longitudinal LDL measurements with generalized mixed models and explored associations with incident ICH using Cox regression analysis.

Results: Statins were prescribed at least once to 75,973 (31%) of the study participants (mean 57 years, 55% females). Among statin users, mean LDL decreased by 3.45 mg/dl per year (95% CI: [-3.47, -3.42]) over follow-up. A higher genetic score of statin response (one SD increment) was associated with significant reductions in LDL levels (-0.05 mg/dl per year, [0.07, -0.02]) and showed concordant effects on other lipid traits as statin use. Over a 14-year follow-up period, a higher genetically predicted statin response among statin users associated with higher ICH risk (HR per one SD increment 1.15, 95% CI [1.04, 1.27]) even after adjusting for statin dose. Among statin non-users, there was no association with ICH risk (p=0.89).

Conclusions: On-statin genetically predicted LDL response is associated with ICH, thus providing further support for the hypothesis that larger LDL declines are causally associated with ICH risk.

Poster Number 78

Raaj Mehta, MD
Medicine, Clinical Research Fellow | rmehta2@mgh.harvard.edu

Gut Microbial Metabolism of 5-ASA Diminishes Its Clinical Efficacy in IBD

INVESTIGATORS: R. S. Mehta, J. R. Mayers, Y. Zhang, N. Glasser, A. Bhosle, L. H. Nguyen, W. Ma, S. Bae, T. Branck, A. N. Ananthakrishnan, E. Franzosa, E. P. Balskus, A. T. Chan, C. Huttenhower

5-aminosalicylic acid (5-ASA) is a commonly used medication to treat inflammatory bowel disease (IBD) but it has variable clinical efficacy. Often compounded for maximal release in the colon, prior data suggests that 5-ASA is metabolized by fecal microbiota into an inactive form. However, no specific human gut microbial enzymes have been identified in 5-ASA conversion or treatment failure. Here, we discover a gut microbial protein superfamily known for its role in fatty acid metabolism that directly inactivates 5-ASA. Among 79 patients with Crohn's disease or ulcerative colitis, we first identified over 2,000 metabolites altered by initiation of 5-ASA treatment, including the clinically ineffective compound, N-acetyl 5-ASA, and other less common derivatives of 5-ASA. Next, in an integrated workflow combining metagenomics, metatranscriptomics, and metabolomics, we identified 12 candidate microbial acetyltransferases from two protein superfamilies for further experimental characterization: thiolase and Acyl-CoA N-acyltransferase. Heterologous expression and biochemical assays on purified enzymes confirmed 5-ASA acetylation by gut microbial thiolases, but not Acyl-CoA N-acyltransferases. Finally, in a cross-sectional case-control study within the discovery cohort, we found that presence of gut microbial thiolases was associated with an increased risk of treatment failure among 5-ASA users. We anticipate that our findings will allow us to predict those who will respond to 5-ASA treatment and may lead to inhibitors of microbial enzymes that can enhance efficacy in non-responders. Furthermore, integrating multi'omics with functional metagenomics for enzyme discovery as in our workflow may help uncover additional mechanistic effects of the microbiome on human health.

Poster Number 79

Livia Parodi, PhD
Neurology, Research Fellow | lparodi@mgh.harvard.edu
Fine-mapping of 1q22 locus in non-lobar ICH

INVESTIGATORS: L. Parodi, M. E. Comeau, J. Chung, G. J. Falcone, R. Malik, D. Woo, C. D. Langefeld, J. Rosand, C. D. Anderson

Spontaneous intracerebral hemorrhages (ICH) are caused by the rupture of small penetrating brain vessels that become affected by cerebral small vessel disease. Genetic risk factors account for 30% of ICH risk and holds the hope of yielding the first drug targets for this condition. A group of variants at the 1q22 locus were the first to by identified by genome-wide association studies. Here we further characterize the genetic architecture underlying ICH susceptibility at 1q22 locus, by performing targeted high-depth sequencing of 1q22 in ICH cases and controls.

The genomic region spanning 1q22, encompassing SEMA4A, SLC25A44 and PMF1/PMF1-BGLAP genes, was sequenced in 1,055 ICH cases and 1,078 controls. Sequencing data were analyzed combining different approaches, considering both rare and frequent variants. Rare Variant Influential Tool (RIFT), was used to evaluate cumulative effects of groups of variants. To further prioritize variants at 1q22, we combined functionally-informed and statistical fine-mapping analysis. Finally, we leveraged publicly available Hi-C data to investigate both chromatin organization and the presence of long-range interactions within the 1q22 locus.

RIFT and fine-mapping analyses prioritized variants in 1q22 active promoter and enhancer regions. Lead variants were predicted altering PMF1 gene expression. Hi-C and ChIA-PET data analysis highlighted high-strength self-interactions between 1q22 genes, as well as the presence of long-range interactions between the 1q22 active promoter and enhancer regions, which appear to regulate PMF1 transcription.

Our data raise the hypothesis that dysregulation of PMF1 expression and consequent impact on polyamine metabolism could underlie the observed higher ICH risk at 1q22 locus.

Poster Number 80

Savvina Prapiadou, MD
Neurology, Graduate Student | sprapiadou@mgh.harvard.edu
Synapse pathways in TBI outcome. A potential therapeutic target?

INVESTIGATORS: S. Prapiadou, L. Parodi, J. M. Rosand, C. D. Anderson

Traumatic brain injury (TBI), a global leading cause of mortality and disability, still lacks effective treatments enhancing recovery. Well-established factors such as age, pre-injury health and injury severity explain only ~35% of the substantial inter-individual outcome variability. Genetics contributes to the residual variability(heritability=0.26), as reported in the first Genome Wide Association Study (GWAS) of TBI outcome. Mechanisms related to synapse maintenance, influencing both synaptogenesis and synaptic pruning, are known to play a role in TBI recovery and impairment.

In the present study we sought to investigate the presence of common mechanisms affecting synapse maintenance shared between TBI and other neuropsychiatric disorders using pathway-enrichment tools and GWAS data, with the goal of highlighting new therapeutic mechanisms for TBI treatment.
A comprehensive literature search was carried out to retrieve a list of pathways involved in synapse maintenance processes. We queried Reactome to generate lists of genes for each candidate pathway. Publicly available GWAS summary statistics of TBI and neurodevelopmental and psychiatric disorders (Schizophrenia, Autism Spectrum Disorder, Major Depressive Disorder, Alzheimer's Disease, and Post-Traumatic Stress Disorder) were used as inputs to perform pathway-enrichment analysis leveraging MAGMAv1.9a, a tool for gene-set analysis. Additional analyses were performed using e-MAGMA and h-MAGMA, allowing the inclusion of functional information, such as gene expression and chromatin organization.

Our strategy allowed us to highlight novel pathway-disease associations, as well as to detect the presynaptic nicotinic acetylcholine receptor as associated with both TBI outcome and schizophrenia, indicating a shared pathological mechanism and therefore a possible therapeutic target for both diseases.

Poster Number 81

Elise Valkanas, BA
Center for Genomic Medicine, Graduate Student | evalkanas@g.harvard.edu

Systematic evaluation of prenatal and pediatric diagnostic yields from whole genome sequencing in autism spectrum disorder and fetal structural anomalies

INVESTIGATORS: E. Valkanas, C. Lowther, J. Giordano, H. Wang, B. Currall, K. O'Keefe, R. Collins, X. Zhao, C. Austin-Tse, E. Evangelista, E. Pierce-Hoffman, C. Whelan, J. Fu, I. Wong, V. Aggarwal, D. Lucente, L. Gauthier, C. Tolonen, N. Sahakian, J. An, S. Dong, M. Norton, T. MacKenzie, N. Vora, B. Levy, H. Brand, R. Wapner, M. Talkowski

Current clinical genetic screening requires multiple methods to evaluate all variant classes, but genome sequencing has the power to transform diagnostic testing by capturing the majority of genetic variation with a single technology. We compared diagnostic yields from genome sequencing to karyotype, microarray, and exome sequencing in a pediatric cohort of 1,612 quartet families with autism spectrum disorder and a prenatal cohort of 175 trios with a structural defect. The diagnostic yield from genome sequencing exceeded all other technologies and provided a ~0.3% additional yield for autism spectrum disorder. In the prenatal samples, we identified a diagnostic variant in 12.0% of cases with negative karyotype and microarray. Here we show genome sequencing is sensitive to the detection of all classes of pathogenic variation captured by three conventional tests and genome sequencing diagnostic yields are to any individual genetic test, warranting consideration of this single technology as a routine first-tier diagnostic approach for autism spectrum disorder and fetal structural anomalies. Overall, the increased diagnostic yield of genome sequencing is modest when compared to the combination of all conventional methods, but is superior to any individual method, thus warranting evaluation as a first-tier screen.compared with HC. Higher PYY may contribute to the lower BMD observed in ARFID.

Poster Number 82

Akiko Yoshinaga, MD
Neurology, Research Fellow | AYOSHINAGA@MGH.HARVARD.EDU

Gene Replacement Therapy in a Schwannoma Mouse Model of Neurofibromatosis Type 2

INVESTIGATORS: A. Yoshinaga, S. Prabhakar, R. L. Beauchamp, E. A. Haidar, A. Stemmer-Rachamimov, D. H. Jung, D. B. Welling, S. R. Plotkin, V. Ramesh, X. O. Breakefield, Neurofibromatosis type 1

Loss of function of the neurofibromatosis type 2 (NF2) tumor suppressor gene leads to the formation of schwannomas, meningiomas and ependymomas, comprising ~50% of all cases of sporadic cases of primary nervous system tumors. Although these tumors are typically benign, they compromise neuronal functions and cause significant morbidity. NF2 syndrome is an autosomal-dominant condition, with bi-allelic inactivation of germline and somatic alleles resulting in loss of function of the encoded protein - merlin (also termed schwannomin) and activation of mTOR pathway signaling in NF2-deficient cells. Standard treatments include surgery and radiotherapy. However, tumor recurrence, and surgical complications necessitate new therapeutic approaches. Here we describe a "gene replacement" approach through direct intratumoral injection of an adeno-associated virus (AAV) vector expressing merlin in a novel human schwannoma model in nude mice. In culture, the introduction of an AAV1 vector encoding merlin (AAV-merlin) into CRISPR-modified human NF2-null arachnoidal cells (ACs) or Schwann cells (SCs) was associated with decreased size in the former, and decreased mTORC1 pathway activation in both, consistent with restored merlin activity. In vivo, a single injection of AAV1-merlin directly into human NF2-null SC-derived tumors growing in the sciatic nerve of nude mice curtailed growth over a 14-week period in comparison to the vehicle injection (compared to controls). These studies establish that merlin re-expression via gene replacement in NF2-null schwannomas is sufficient to suppress tumor growth, thereby potentially providing a more effective treatment for NF2.

Poster Number 83

Christopher Alba, BS
Medicine, Research Assistant | calba1@mgh.harvard.edu

Cost-effectiveness of broadly neutralizing antibodies for HIV prophylaxis for all infants born in high-burden settings

INVESTIGATORS: C. Alba, S. Malhotra, S. Horsfall, M. Barnhart, K. Chapman, C. K. Cunningham, P. Fast, G. G. Fouda, K. A. Freedberg, L. Ghazaryan, V. Leroy, C. Mann, M. M. McCluskey, E. J. McFarland, V. Muturi-Kioi, S. R. Permar, D. Sok, L. Stranix-Chibanda, M. C. Weinstein, A. L. Ciaranello, C. M. Dugdale

BACKGROUND: Approximately 150,000 infants acquire HIV annually. We evaluated the potential clinical impact and cost-effectiveness of offering anti-HIV broadly neutralizing antibody (bNAb) prophylaxis, once clinically approved, to infants in high-burden settings.

METHODS: We simulated birth cohorts in Côte d'Ivoire, South Africa, and Zimbabwe using the Cost-Effectiveness of Preventing AIDS Complications model. We modeled strategies offering one, two, or extended (through 18 months) bNAb doses to infants: a) with known, WHO-defined high-risk HIV exposure at birth (HR-HIVE), b) with known exposure at birth (HIVE), or c) regardless of exposure (ALL). Doses were offered at three-month intervals starting at birth. Eligible infants also received standard-of-care prophylaxis per WHO recommendations. Base-case inputs included 70% bNAb efficacy (sensitivity analysis range: 10-100%), 3-month efficacy duration (1-6 months), and $20/dose cost ($5-$100/dose). Outcomes included infant HIV infections, life expectancy, lifetime HIV-related costs, and incremental cost-effectiveness ratios (ICERs, in US$/year-of-life-saved; cost-effectiveness threshold: ≤50% GDP per capita).

RESULTS: Under base-case assumptions, HIVE and ALL strategies would prevent 6-26% and 10-42% of current infant HIV infections, respectively, across settings. HR-HIVE strategies would result in greater costs and smaller life expectancy gains than HIVE strategies. At most bNAb costs and efficacies assessed, HIVE strategies would be cost-effective in Côte d'Ivoire and Zimbabwe, and ALL strategies would be cost-effective in South Africa, partially driven by higher maternal HIV prevalence.

Poster Number 84

Camille Andre, MS
Ophthalmology, Graduate Student | candre2@meei.harvard.edu

Characterization of the resistome in gram-positive bacteria causing keratitis.

INVESTIGATORS:C. ANDRE, M. S. GILMORE, P. BISPO

Antimicrobial resistance (AMR) in microbial keratitis is a concerning issue that can result in treatment failure. The aim of this study was to characterize phenotypically and genomically the AMR patterns of gram-positive-bacteria (GPB) isolated from keratitis at MEEI.

Whole-Genome-Sequencing was performed on 161 GPB keratitis isolates using Illumina HiSeq. Molecular typing was performed by MLST. CARD algorithm was used to identify genes that confer AMR. Minimum inhibitory concentrations were determined by broth microdilution.

Staphylococcus aureus was the most common pathogen (53.4%) and its population structure was dominated by lineages grouped within the clonal complex 5 (32.6%), which includes epidemic MRSA strains commonly associated with multidrug-resistant (MDR) infections. Resistance to antibiotics was more prevalent among MRSA isolates, with rates of resistance higher than 70% for fluoroquinolones (FQ) and azithromycin. The newest FQ (besifloxacin-moxifloxacin) had lower MIC90 compared with the earlier ones. More than 30% of coagulase-negative-Staphylococcus were resistant to FQ and half of them were resistant to azithromycin (52.9%). High FQ resistance was associated with several mutations in the gyrA and parC genes. CARD analysis revealed that 26.7% of S.aureus co-harbored ant(9)-Ia and ermA genes that confers resistance to aminoglycosides, and to macrolides-lincosamides-streptogramin B, localized in a Tn554 transposon. Among S.pneumoniae isolates, resistance rates were less than 10% to all antibiotics tested except for ofloxacin (14.4%), azithromycin (30.8%) and penicillin (30.8%).

We provided an overview of current rates of resistance to antibiotics commonly used to treat keratitis caused by GPB and a characterization of the associated molecular mechanisms that confer AMR.

Poster Number 85

Nicole Belanger, BA
Ophthalmology, Research Technician | nicole_belanger@meei.harvard.edu

Molecular Characterization of Fungal Endophthalmitis and Keratitis caused by Yeasts

INVESTIGATORS: N. L. Belanger, P. Bispo

Endophthalmitis and keratitis are serious, sight-threatening conditions. In the northeast region of the U.S., most fungal ocular infections are caused by yeasts, and despite their relevance, little is known about the molecular epidemiology of these infections. From 2014-2021, there were a total of 38 yeast isolates collected from cases of endophthalmitis and keratitis at Massachusetts Eye and Ear. The isolates were speciated by ITS1/ITS2 sequencing and the C. albicans isolates were multilocus sequence typed (MLST) to determine population structure. ITS sequencing demonstrated that this population was dominated by Candida spp. (37 out of 38; 97%), with 58% of the cases being caused by C. albicans (n=22), and the remaining associated to emerging non-albicans species with a predominance of C. parapsilosis (n=8) and C. dubliniensis (n=6), and one isolate of C. tropicalis. One isolate was identified as Clavispora lusitania. MLST analysis of the 22 C. albicans isolates showed a heavy prevalence of CC69, with 54% (n=12) of them belonging to this clonal complex and a slightly higher predominance among endophthalmitis (8 out 12; 66%). Additionally, there were two isolates belonging to the CC90 complex, and four singletons: STs 334, 602, 3139, and 3633. The remaining 4 isolates were submitted as new sequence types. In conclusion, we observed that nearly half of the ocular infections caused by yeasts are associated with C. albicans, with evidence for the emergence of non-albicans species as important causes of infection. These strains clustered mainly within the CC69, which seem to be particularly fit to cause endophthalmitis.

Poster Number 86

Jodian Pinkney, MBBS
Medicine, Research Fellow | jpinkney@mgh.harvard.edu

COVID-19 vaccine uptake, vaccine hesitancy and medical mistrust among reproductive-aged women in Jamaica

INVESTIGATORS: J. A. Pinkney, K. Carroll, L. Bryan, G. Witter, E. Hyle, B. Ojikutu, L. Bogart

Background
Little is known about COVID-19 vaccine uptake, vaccine hesitancy and medical mistrust among reproductive-aged women in Jamaica.

Methods
We conducted a cross-sectional, web-based survey of all reproductive-aged women (patients, providers, and staff) at a tertiary care hospital in Jamaica from February 1- 28, 2022 to assess COVID-19 vaccine receipt, hesitancy (defined as a delay or refusal of vaccines despite availability of vaccine services) and medical mistrust (e.g., "I don't trust the COVID-19 vaccine"). We used multinomial logistic regression to predict vaccination, hesitancy, and mistrust in pregnant versus non-pregnant women, adjusting for age, education, and comorbidities.

Results
100 reproductive-aged women responded between February 1-2, 2022. 41% were pregnant and 59% were non-pregnant. Pregnant women were younger than non-pregnant women [M(SD) = 29.5 (±7.2) and 35.6 (±7.1), respectively]. Vaccine uptake among pregnant women was 34% compared with 83% among non-pregnant women, (AOR=0.11, 95%CI=0.03 – 0.437; p=0.001). Pregnant women were more likely to agree with several mistrust statements compared with non-pregnant women including "I don't trust the COVID-19 vaccine" (AOR=3.67, 95%CI=1.07 – 12.6; p=0.039).

Conclusion
Preliminary findings suggest that pregnant women in Jamaica may be less likely to get vaccinated compared with non-pregnant reproductive-aged women. Pregnant women may also have higher levels of mistrust. Rapid dissemination of pregnancy-related COVID-19 vaccine safety data, by trusted sources, may lead to improved vaccine uptake in this group.

Poster Number 87

Kelsey Wheeler, PhD
Surgery, Research Fellow | kwheeler5@mgh.harvard.edu
The role of bacterial communication pathways in infection and dysbiosis

INVESTIGATORS: K. M. Wheeler, L. G. Rahme

The human microbiota is a complex ecosystem populated by trillions of bacteria, viruses, and fungi that defend against invading pathogens. Infections are often treated with antibiotics; however, broad-spectrum antibiotics cannot differentiate between pathogens and beneficial microbes, leaving the host susceptible to secondary infection. Moreover, antibiotics create a selective pressure that drives the evolution of resistance. In fact, some pathogens are resistant to all existing antibiotics, making infections recalcitrant to conventional therapies and leading to high mortality. Thus, a critical question emerges: How can we treat infections without altering the microbiota and driving the spread of antibiotic resistance? By leveraging clinical isolates of the pathogen Pseudomonas aeruginosa, a bacterial mutant library, and a fruit fly infection model, we identify specific pathogen-commensal interactions that are relevant to pathogen colonization. We further show that disrupting bacterial communication pathways (i.e., quorum sensing) limits pathogen colonization and infection, in part, by regulating interactions between pathogens and commensals. We then demonstrate the therapeutic potential of disrupting these pathways with a novel quorum sensing inhibitor. Results from this dynamic setting may have an immense impact on the fight against antibiotic resistance and provide insights into microbial competition in vivo.

Poster Number 88

Eftitan Akam, MD
Pediatrics, Resident | eyakam@partners.org
Race and Ethnicity-Based Bias in Bedside Nursing Notes

INVESTIGATORS: E. Y. Akam, F. C. Stanford

Background: Clinician documentation communicates vital information on patients and their care. Research has demonstrated that bias can be transmitted between providers through simulated clinical documentation, yet there are few studies directly assessing implicit bias in clinician notes. Nursing notes for inpatient pediatric patients frequently include information on the patients' bedside companions. We hypothesized that racial bias exists in pediatric nursing notes, and that white patients, compared to minority patients, would have a higher percentage of positive descriptors.

Methods: Notes for patients <18 years old admitted in 2018 were analyzed. Records were excluded if there was mention of state custody involvement or if race was unknown. Each encounter was manually reviewed and coded for valence (positive, negative, neutral) by a single individual blinded to the patient's race. A chi-square goodness of fit test was performed to assess for differences in proportions of positive versus negative or neutral encounters by race.

Results: 21,949 encounters were evaluated. Black patients constituted 16% of encounters, Hispanic 3%, 'other' 25%, and white 56%. Chi-square test of the distribution of valence (positive vs neutral or negative) indicated significant differences based on racial category ($x2 = 56$, $p < 0.0001$). Post-hoc adjusted analyses revealed significant decrease in positive valence for black and 'other' patients, and significant increase in positive valence for white patients.

Conclusion: These findings suggest that clinicians demonstrate implicit bias in their descriptions of the bedside companions of pediatric patients. Further studies are needed to better understand the effects of these biases on patient care.

Poster Number 89

Alyssa Amick, MPH
Medicine, Research Specialist | aamick1@mgh.harvard.edu
Cost-effectiveness of HIV PrEP among young men who have sex with men in the US

INVESTIGATORS: A. K. Amick, G. E. Eskibozkurt, S. G. Hosek, C. F. Flanagan, R. J. Landovitz, K. A. Freedberg, C. M. Wilson, M. C. Weinstein, A. D. Paltiel, A. L. Ciaranello, A. M. Neilan

In the Adolescent Medicine Trials Network for HIV/AIDS Interventions (ATN) studies 110/113, oral tenofovir-based (F/TDF) HIV pre-exposure prophylaxis (PrEP) was safe and feasible among young men who have sex with men (YMSM), ages 13-24. However, the clinical and economic consequences of PrEP in this low-adherence/low-retention population are uncertain.

Using a microsimulation model, we modeled a US YMSM population to compare 1) Annual HIV screening and 2) PrEP with quarterly HIV screening over 10-year and lifetime horizons. Model-projected outcomes included: primary transmissions, quality-adjusted life years (QALY), costs, and incremental cost-effectiveness ratios (ICER). Sensitivity analyses included varying: annual drug price of PrEP ($0-branded: $9,000) and HIV incidence (as low as 0.01/100 person-years, i.e., a population without identified HIV risk factors).

Compared to annual HIV screening, generic PrEP would increase QALYs (8.37 to 8.42), reduce new HIV infections (40% to 35%), and decrease costs (by $14,000) over 10 years. Generic PrEP would be cost-saving at HIV incidences off-PrEP ≥2/100PY (over 10 years) and ≥0.5/100PY (lifetime). At branded PrEP drug price, PrEP would increase costs by $15,000 over a 10-years (ICER: $318,000/QALY, cost-saving over a lifetime). PrEP would not be cost-effective at any price point in a population with HIV incidence <0.1/100PY.

In a population of YMSM at increased risk of HIV infection, PrEP would be cost-saving compared to annual screening alone, despite low retention and adherence. At generic PrEP prices, PrEP would be cost-saving over a lifetime even at HIV incidences lower than observed among YMSM enrolling in ATN 110/113.

Poster Number 90

Oluwafemi Balogun, MBBS, MPH
Medicine, Researcher/Data Analyst | obalogun@mgh.harvard.edu
Role of Metformin in Reducing Hepatic Fibrosis Among Non-Diabetic Patients with Non-alcoholic Fatty Liver Disease

INVESTIGATORS: E. S. Shaikh, J. Y. Wang, S. Stoyanova, Z. N. Memel, T. G. Simon, K. E. Corey

Metformin, an insulin sensitizer, is frequently prescribed to individuals with type 2 diabetes mellitus (T2D). The role of the medication in managing non-alcoholic fatty liver disease (NAFLD) among diabetic individuals has been well demonstrated in the literature. However, studies on the association between metformin usage and hepatic fibrosis in individuals without T2D remain limited. We aimed to explore the association between the use of metformin and risk for prevalent fibrosis among non-diabetic patients with NAFLD. Methods We conducted a cross-sectional observational study on 186 non-diabetic individuals 18 years and above with a known diagnosis of NAFLD. A two-to-one matching on age, gender, and metabolic syndrome was done using propensity-based scoring to evaluate the average effect of metformin treatment on study participants. In addition, bivariable and multivariable logistic regression models were developed to explore the associations between metformin use and outcome (risk for hepatic fibrosis as assessed by the FIB-4 index). We matched 124 (37.6%) participants in the control group with the participants in the metformin group (n=62). The therapeutic use of the biguanide in non-diabetics was protective against fibrosis (aOR 0.44, 95% CI 0.21 – 0.90) in the multivariable logistic regression model. Total Bilirubin level (aOR 2.90, 95% CI 1.58 – 5.38). In this study, metformin use demonstrated a decreased likelihood for fibrosis in non-diabetic patients with NAFLD. Moving forward, a randomized control trial examining the impact of metformin on patients with non-diabetic NAFLD will help examine this relationship further.

Poster Number 91

Bethany Cucka, BS
Dermatology, Clinical Research Fellow | bcucka@mgh.harvard.edu

Analysis of dermatology consultation follow-up after Emergency Department evaluation: an assessment of disparities and potential interventions to increase post-discharge care among vulnerable populations

INVESTIGATORS: B. Cucka, B. Biglione, S. Chand, G. Smith, B. Yun, D. Kroshinsky

Background: The Emergency Department (ED) is a frequent source of care for patients with dermatologic disease, likely owing to limited access to routine and urgent outpatient dermatologic care. Patients without adequate follow-up planning are at risk for re-presentation.

Objective: To identify predictors of post-discharge visit attendance and risk factors for re-presentation among patients who seek ED care for dermatologic issues.

Methods: A retrospective chart review of 152 patients who had a dermatology consultation ordered while in the ED.
Results: An electronic referral resulted in most appointments being scheduled and ultimately attended. Expecting the patient to call on their own resulted in the lowest rates of scheduled appointments. Risk factors for not attending a scheduled appointment include being widowed, unemployed, and having unstable housing. 10.5% of patients re-presented to the ED within 30 days. Significant predictors of re-presentation included frequent ED history, initial refusal of treatment (most commonly leaving AMA), and Black or African American race.

Limitations: Data collection was retrospective, potentially result in missing data or information bias.
Conclusion: Positive predictors of post-discharge visit attendance include stable housing, not being unemployed, and not being widowed. Patients who refuse treatment, identify as Black or African American, and have a frequent ED history are at risk for re-presenting.

Poster Number 92

Tolulope Famuyiro, MD, MPH
Medicine, Clinical Research Fellow | tfamuyiro@mgh.harvard.edu

Extended Length of Stay in Older Adults with Hip Fracture: A Descriptive Report

INVESTIGATORS: T. B. Famuyiro, C. T. Pu, C. S. Ritchie, O. Ahredsen, E. Franco-Garcia

Background: Extended length of stay (ELOS) in the US is defined as hospital stay greater than 6.1 days. ELOS contributes to hospital bed occupancy and resource utilization. Identifying factors that contribute to ELOS in older adults could help reduce healthcare spending and the burden of hospitals reaching full capacity.

Objective: To identify factors contributing to ELOS in older adults with hip fracture who underwent operative repair at an academic tertiary hospital.

Methods: We reviewed the charts of patients aged 65+ years who were admitted between August and October 2021 to the orthopedic trauma-geriatrics co-managed care service for operative hip fracture repair. We stratified patients into those with and without ELOS. Using logistic regression analysis, we assessed for independent risk factors (age, frailty, nutritional status, etc.) that could impact LOS. We also used frequencies and percentages to categorize the most common barriers delaying discharge.

Results: Out of 82 total admissions, 56 patients met inclusion criteria. Mean age of patients was 81.7 (± 10.1) years; 57% were female. Mean LOS in those with and without ELOS was 9.5 (± 2.5) and 4.8 (± 1.0) days respectively. LOS was not significantly impacted by age, pre-admission from nursing facility or home, presence of malnutrition, positive frailty screen, or cognitive impairment. Post-operative medical complications (delirium, anemia, congestive heart failure--62%) and discharge coordination (insurance authorization and discharge placement delay--29%) contributed to ELOS.

Poster Number 93

Anna Handorf, MD
Pediatrics, Research Fellow | ahandorf@mgh.harvard.edu

The TinyTalks Curriculum: Developing Chalk-Talk Style Videos to Support Today's Learners

INVESTIGATORS: M. Healy, W. Tan, I. Moawad, K. Dzara, W. Hardiman, A. Lu, A. Klouda, A. Frey-Vogel

Background: On busy rotations, educational opportunities must consider learner needs. Today's learners prefer short, self-directed, on demand learning that incorporates technology. Despite these preferences, the pediatric residency's curriculum involves traditional didactics.

Objective: Use Kern's 6-step approach to curriculum development to create a curriculum incorporating technology to meet the learning needs of pediatric residents.

Methods: Using a literature review and broad needs assessment (step 1), we identified the problem. Results of a targeted needs assessment survey of pediatric residents (step 2) informed goals, objectives, and educational strategies (steps 3,4). We are developing and implementing a curriculum of chalk-talk videos (step 5), with plans to evaluate its effectiveness (step 6).

Results: Pediatric residents are dissatisfied with the current curriculum. Based on the literature, we are creating a comprehensive online curriculum of short, chalk-talk videos. 44/64 (69%) pediatric residents completed the needs assessment indicating perceived learning deficiencies, desired topics and teachers, and preferred methods of engaging the curriculum. Residents reported being least knowledgeable in genetics, allergy/immunology, and rheumatology. The most requested content was nephrology, pulmonology, cardiology, and dermatology. Residents requested teachers from six interprofessional disciplines. 73% of residents envisioned using the curriculum for independent study. We created five short training videos about preparing chalk-talk videos. Four physicians and one pharmacist are creating pilot videos.

Conclusions: Guided by Kern's framework, we are developing a comprehensive curriculum of short, chalk-talk style videos of clinical pearls taught by interprofessional clinicians that can be used flexibly by pediatric residents. We call

Poster Number 94

Hyunjoon Lee, MS
Center for Genomic Medicine, Senior Data Analyst | hlee82@mgh.harvard.edu

Patterns and predictors of psychiatric care utilization during the COVID-19 pandemic among at-risk individuals in a major health system

INVESTIGATORS: H. Lee, K. W. Choi, A. Tu, J. L. Restivo, C. H. Liu, J. A. Naslund, V. Patel, J. W. Smoller, Massachusetts Consortium on Pathogen Readiness

Little is known about the mental health care-seeking of individuals with pre-existing mental illness during a pandemic. This study leveraged large-scale electronic health record (EHR) data to describe and predict psychiatric care utilization among individuals with pre-existing mental illness during the COVID-19 pandemic.

Using the Mass General Brigham EHR, we identified three patient groups based on a history of (1) stress-related disorders (e.g., depression, anxiety) (N=113,209) (2) severe mental disorders (e.g., psychotic or bipolar disorders) (N=11,327), or (3) psychiatric disorders characterized by compulsive behavior (e.g., OCD, eating disorder) (N=6,712) within 6 months before the pandemic (9/14/2019 - 3/12/2020). Three corresponding reference groups (N=110,262, 11,507, 6,068, respectively) were identified for the prior year (9/14/2018 - 3/12/2019). Psychiatric care utilization was defined as number of patient visits from 3/13 through 12/31 in each year. We also used cross-validated machine learning methods (ridge, lasso, elastic net) to identify demographic and clinical predictors of higher psychiatric care utilization.

For all three patient groups, the number of psychiatric care visits was significantly lower in March 2020 than prior year (6, 14, 15% fewer visits, respectively) but rapidly increased starting April, and by August was significantly higher than prior year (15, 21, 37% more visits, respectively). The number of visits was disproportionately higher than prior year relative to the number of patients seen. Patient groups exhibited distinct sets of clinical predictors.

Among patients with pre-existing mental illness, psychiatric care utilization significantly increased during the pandemic. Pre-existing medical comorbidities may help identify at-risk individuals with higher utilization.

Poster Number 95

Natalie McCormick, PhD
Medicine, Research Fellow | nmccormick@mgh.harvard.edu

What Drives Racial Disparities in Gout in the US? – Population-Based, Sex-Specific, Sequential Casual Mediation Analysis

INVESTIGATORS: N. McCormick, N. Lu, C. Yokose, A. D. Joshi, Y. Zhang, H. K. Choi

Background: Traditionally viewed as a disease of White men, emerging cohort data suggest gout imparts an even larger burden on Blacks, but general population data are lacking.

Objective: Determine and quantify sex-specific mediators of racial disparities in gout prevalence among nationally representative sample of US adults.

Methods: Using 2007-2016 National Health and Nutrition Examination Survey data, we conducted sequential causal mediation analysis (adjusting for upstream mediators) to determine proportion of racial differences in gout prevalence attributable to 7 potentially mediating factors: low education, poverty, body mass index (BMI), alcohol, low-quality diet, diuretic use, and chronic kidney disease (CKD: eGFR <60 mL/min, using latest equations without coefficient for Black race).

Results: Age-standardized gout prevalence was 3.5% vs. 2.0% in Black and White women, respectively (age-adjusted OR=1.8 [95% CI: 1.3-2.5]), and 7.0% vs. 5.4% in Black and White men (OR=1.3 [1.0-1.6]). BMI levels were higher, and poverty more frequent, in Black women (vs. White), but similar between Black and White men. Alcohol consumption was lower in Blacks than Whites.

Largest mediating factor of excess gout cases among Black women was excess BMI (56% of the racial difference, independent of education, poverty, diet, and alcohol), followed by CKD (24%), poverty (17%), and diet quality (12%).

CKD was largest mediator among men (46%), followed by diet (20%) and diuretics (14%); proportions from BMI (12%) and poverty (0.5%) were far smaller.

Conclusion: Efforts aimed at improving adiposity, diet quality, and kidney disease, while recognizing impact of poverty in female gout, may help reduce these disparities.

Poster Number 96

Alex McDowell, MPH, MS, PhD, RN
Medicine, Research Fellow | amcdowell4@mgh.harvard.edu

Effect of State-Level Insurance Policies on Use of Gender Affirming Surgery in Massachusetts

INVESTIGATORS: A. McDowell, V. Fung

Introduction: Access to gender affirming health care improves well-being for transgender and gender diverse (TGD) individuals. Massachusetts has implemented policies to increase coverage of gender affirming care for individuals with commercial insurance and MassHealth. We use the Massachusetts All Payer Claims Database to estimate the effect of these policies on utilization of gender affirming surgeries among TGD individuals.

Study Design: We employed a validated algorithm that uses gender-related diagnosis codes to identify TGD individuals, 2012-2016. With difference-in-differences design, we compared changes in billed utilization of gender affirming surgeries among TGD individuals with MassHealth and commercial insurance versus a comparison group of TGD individuals in self-insured commercial insurance plans, which are exempt from the policies of interest.

Findings: The study included 2,191 TGD individuals with MassHealth; 1,413 in commercial plans; and 1,103 in the comparison group. In the pre-policy period, 2.2% of TGD individuals with MassHealth vs. 5.2% of the comparison group had any gender affirming surgery; post-policy, this grew to 6.3% in MassHealth vs. 7.4% in the comparison group (OR=2.17, 95%CI: 1.77-2.57). Among TGD individuals in commercial plans, changes in use of gender affirming surgery post- vs. pre-policy did not significantly differ from the comparison group (OR=1.13, 95%CI=0.46-1.81).

Conclusions: A policy requiring MassHealth coverage of gender affirming services increased use of gender affirming surgeries that are associated with improvements in health for TGD individuals. In contrast, a state-level ban on categorical exclusion of gender affirming care from commercial insurance policies was not associated with increased use of gender affirming surgery.

Poster Number 97

Jinho Park, PhD
Center for Systems Biology, Research Fellow | jpark93@mgh.harvard.edu
Robust detection of optical signal for lateral flow biosensors

INVESTIGATORS: J. Park, E. Park, Y. Cho, I. Shin, H. Lee

Lateral flow assays (LFAs) are widely adopted for fast, on-site molecular diagnostics. Obtaining high-precision assay results, however, remains challenging and often requires a dedicated optical setup to control the imaging environment. Here we de-scribe qLiNE (quick Light Normalization Exam) that transforms ubiquitous smartphones into a robust LFA reader. qLiNE used a reference card, printed with geometric patterns and color standards, for realtime optical calibration: a photo of a LFA test strip was taken along with the card, and the image was processed by a smartphone app to correct shape distortion, illumination brightness, and color imbalances. This approach yielded consistent optical signal, enabling quantitative molecular analyses under different illumination conditions. We adapted qLiNE to detect cortisol, a known stress hormone, in saliva samples at point-of-use settings. The assay was fast (15 min) and sensitive (detection limit, 0.16 ng/mL). Serial qLiNE as-say detected diurnal cycles of cortisol levels as well as stress-induced cortisol increase.

Poster Number 98

Robert Regenhardt, MD, PhD
Neurosurgery, Clinical Research Fellow | robert.regenhardt@mgh.harvard.edu
Large vessel occlusion stroke transfers achieve faster arrival-to-puncture times and improved outcomes with direct-to-endovascular suite protocol

INVESTIGATORS: R. W. Regenhardt, J. A. Rosenthal, A. A. Dmytriw, J. E. Vranic, A. K. Bonkhoff, M. Bretzner, J. A. Hirsch, J. D. Rabinov, C. J. Stapleton, A. B. Patel, A. B. Singhal, N. S. Rost, T. M. Leslie-Mazwi, M. R. Etherton

PoIntroduction: For patients with large vessel occlusion (LVO) stroke, time to treatment with endovascular thrombectomy (EVT) is crucial. We sought to evaluate the arrival-to-puncture times and outcomes for transferred patients accepted directly to the angio-suite (LVO2OR) versus those accepted through the emergency department (ED) in a hub-and-spoke telestroke network.

Methods: Consecutive patients transferred for EVT with spoke CTA-confirmed LVO, spoke ASPECTS >6, and LKW-to-hub arrival <6 hours were identified. Our LVO2OR protocol began implementation in January 2017. The LVO2OR cohort includes patients who underwent EVT from July 2017 to October 2020; the ED cohort includes those from January 2011 to December 2016. Arrival-to-puncture time and 90-day modified Rankin Scale (mRS) were prospectively recorded.

Results: The LVO2OR cohort was comprised of 91 patients, and the ED cohort 90. LVO2OR patients had more atrial fibrillation (AF, 51% vs 32%, p=0.02) and more M2 occlusions (27% vs 10%, p=0.01). LVO2OR patients had faster median hub arrival-to-puncture time (11 vs 92 minutes, p<0.001), faster median telestroke consult-to-puncture time (2.4 vs 3.6 hours, p<0.001), greater TICI 2b-3 reperfusion (92% vs 69%, p<0.001), and greater 90-day mRS <2 (35% vs 21%, p=0.04). In a multivariable model, LVO2OR significantly increased the odds of 90-day mRS <2 (aOR 2.77, 95%CI 1.07,7.20; p=0.04) even when controlling for age, baseline mRS, AF, NIHSS, M2 location, and TICI 2b-3.

Conclusion: In a hub-and-spoke telestroke network, accepting transferred patients directly to the angio-suite was associated with dramatically reduced arrival-to-puncture time and may lead to improved 90-day outcomes.

Poster Number 99

Alexander Soltoff, BS
Medicine, Research Coordinator | asoltoff@mgh.harvard.edu

Factors Influencing Palliative Care for American Indians in the Great Plains: A Qualitative Study of Providers Association of Neighborhood Factors with Pediatric Asthma Disparities

INVESTIGATORS: A. E. Soltoff, B. R. Daubman, K. A. Armstrong, S. Purvis, M. Ravicz, G. Johnson, T. Duran, M. Sargent, Great Plains Lakota Research Collaborative

Summary: There is a significant disparity in access to palliative care (PC) services for people living rurally in the United States as compared to their urban-dwelling counterparts. This disparity is even greater for patients experiencing serious illness in American Indian Reservation communities. To better understand factors influencing PC access and delivery for American Indians residing on reservations and to inform the development of culturally tailored PC interventions, we performed qualitative interviews with 38 primary and subspecialty providers in the Great Plains. Using a semi-structured interview guide, we explored challenges, needs, and facilitators of care for seriously ill patients. Interviews were recorded and transcribed verbatim. Thematic analysis of transcripts was performed to identify four broad factors influencing PC for Reservation-dwelling patients. Factors included: 1) rural geography, 2) fragmentation of services, 3) staffing limitations, 4) historical trauma and racism.

Main Conclusions: The provision of PC for patients living in rural Reservation Communities is dependent on building trust, smooth coordination of care, and the elimination of travel barriers. Historical trauma and racism over generations have created deep mistrust in the medical system. Stabilizing the primary workforce and integrating care between primary and specialty facilities is a critical first step towards rebuilding trust with the Reservation-dwelling population. Leveraging telehealth services in the provision of palliative care represents one solution to overcoming travel barriers. Community-based navigators could play a key role in linking patients to palliative resources on the reservations and strengthening continuity of care. uptake. This presentation outlines preliminary findings shared in February 2021 with key local, state, and national stakeholders for rapid intervention in marginalized communities in the state of California.

Poster Number 100

Zhiyou Yang, PhD
Medicine, Data Analyst | zyang15@mgh.harvard.edu

Enrollment Patterns in Fully Integrated Dual-Eligible Special Needs Plans Among Elderly Beneficiaries in Massachusetts

INVESTIGATORS: Z. Yang, J. Hsu, J. Newhouse, V. Fung

There are numerous efforts at the federal and state levels to better integrate Medicare and Medicaid coverage for dual-eligible enrollees. An increasing number of duals are enrolling in Dual-eligible Special Needs Medicare Advantage plans (D-SNPs), but there is less evidence on enrollment stability in D-SNPs.

We used the Massachusetts All Payer Claims Database (MA APCD), 2012-2016, to identify dual-eligibles who enrolled in Senior Care Options (SCO) anytime during 2014. Among new SCO enrollees in 2014, we examined the proportion who left SCO plans over 24 months. Using linear probability models, we examined demographic, clinical, and utilization characteristics associated with switching from SCO to traditional Medicare in the first 12 months vs. staying in SCO.

We show that SCO enrollment grew steadily between January 2012 (15,537) and December 2016 (43,153). Among 35,816 SCO enrollees in 2014, 24% were new enrollees. About one-in-eight elderly dual-eligibles in fully integrated D-SNPs in Massachusetts in 2014 left within the first 12 months of enrolling. Among enrollees who left SCO for traditional Medicare in the first year, switching rates were lower among those with a hospitalization, but higher among those with mental health conditions and heart failure.

Since the study period, Medicare has limited the enrollment windows for dual-eligibles from monthly to quarterly. Work is needed to understand beneficiaries' reasons for switching out of D-SNPs as short tenure in plans could decrease continuity of care for beneficiaries and integration incentives for plans.

Poster Number 101

Yousef Badran, MD
Medicine, Clinical Research Fellow | yousef.badran@mgh.harvard.edu

Concurrent immune checkpoint inhibition and selective immunosuppressive therapy in patients with immune-related enterocolitis

INVESTIGATORS:Y. R. Badran, F. Zou, S. M. Durbin, B. E. Dutra, H. A. Sbeih, A. S. Thomas, M. Altan, J. A. Thompson, W. Qiao, D. E. Leet, P. Y. Lai, N. K. Horick, M. Postow, D. M. Faleck, Y. Wang, M. Dougan

Immune checkpoint inhibitor (ICI) therapy is often suspended because of immune-related enterocolitis (irEC). This is the first and largest multi-center study of treatment for irEC with concurrent selective immunosuppression (infliximab or vedolizumab) in combination with ICI therapy to facilitate ongoing cancer treatment and reduce irEC recurrence.

Conclusions:
Here we show that after resolution of irEC symptoms, re-initiation of ICI with concurrent vedolizumab is associated with a lower rate of symptom recurrence (14.3%) compared to treatment with concurrent infliximab (46.9%) or no colitis treatment (36.9%) (p-0.006). The severity of symptoms on recurrence was lower in patients concurrently treated with SIT. SIT toxicities were highest in patients receiving infliximab and the most common were infusion reactions (3 events). There was a trend towards worse survival outcomes in patients treated with concurrent infliximab. This work emphasizes the importance of conducting prospective, placebo-controlled trials that compare current regimens used for treatment of immune related adverse events (irAEs) as well as resumption of ICI after irAEs.

Poster Number 102

Ferran Barrachina, BS, MS, PhD
Medicine, Research Fellow | fbarrachinavillalonga@mgh.harvard.edu

The absence of CX3CR1 impairs immune surveillance in the epididymis

INVESTIGATORS: F. Barrachina, K. V. Ottino, L. J. Tu, S. Breton, M. A. Battistone

Spermatozoa acquire motility and fertilizing power during their transit through the epididymis, an organ located downstream of the testis. Mononuclear phagocytes (MPs) play an active role in the immunological homeostasis of the epididymis. We previously showed that epididymal CX3CR1+MPs can internalize and process circulatory antigens. Here, we examined whether the lack of functional CX3CR1 in homozygous mice (CX3CR1EGFP+/+) alters the ability of MPs to initiate immune responses against harmful antigens during epididymitis.

Confocal microscopy showed that intraepithelial MPs located in the epididymis from CX3CR1EGFP+/+ mice displayed a significant reduction in the number of luminal-reaching projections. Immunophenotype characterization showed no differences in the percentage of macrophages or dendritic cells between CX3CR1EGFP+/+ and control MPs. Flow cytometry showed no overall impairment in antigen capture 1h after ovalbumin-Alexa 647 injection, however, confocal microscopy revealed reduced internalization specifically in intraepithelial CX3CR1EGFP+/+ cells. We also observed a higher number of MPs with a monocytic signature and a CD103+ dendritic cell accumulation in the CX3CR1EGFP+/+ epididymis after epididymal injection of lipopolysaccharide.

Here we show morphological alterations in luminal intraepithelial projections in MPs from CX3CR1-deficient mice, which displayed an impaired antigen sampling, and an immunophenotypic shift in response to injury. Additionally, our results indicate that CX3CR1 deletion induces defective cell-cell communication between MPs and CD103+ cells, and support the hypothesis that MPs are the gatekeepers of the immunological blood-epididymis barrier by surveying antigens. By identifying immune mechanisms required for antigen sampling and presentation, our study may lead to new therapies for male infertility associated with immunological disorders.

Poster Number 103

Caitlin Burk, MD
Medicine, Research Fellow | cmburk@mgh.harvard.edu

IFNG is constitutively expressed by esophagus-resident CD8+ T cells and is poised to mediate a disease-specific effect via its action on IFNGR+ eosinophils during active EoE

INVESTIGATORS: C. M. Burk, D. M. Morgan, B. Ruiter, Q. Yuan, J. C. Love, W. G. Shreffler

Recent whole tissue RNA sequencing (RNAseq) and other bulk assays indicate that type I and II interferon responses are upregulated in active eosinophilic esophagitis (EoE), a Th2-biased inflammatory disease, but the cellular signaling network is unresolved. Using an existing single-cell RNAseq dataset derived from esophageal and duodenal biopsies from 10 pediatric subjects with EoE, we identified differentially expressed genes using FindMarkers in the Seurat package. We compared both esophageal versus duodenal expression, and active disease versus remission in the esophagus. We focused on interferon signaling genes and interferon response genes previously found to be upregulated in EoE. Here we show that esophageal interferon gamma (IFNG) expression is predominantly by a cluster of majority-CD8+ T cells and is constant in active and remission disease states. IFNG receptor (IFNGR) subunits as well as many response genes are upregulated in active disease – the latter being mostly in the esophageal epithelium ($p < 0.01$). Using pseudobulk analysis, we show that the expression of IFNGR on eosinophils is being responsible for its overall differential expression in active disease versus remission. In conclusion, CD8+ T cells are the major source of esophageal IFNG in subjects with EoE and the differential expression of IFNGR in active disease is due to the presence of eosinophils. While IFNG expression was constitutive, a subset of interferon response genes was upregulated in epithelium during active disease. We hypothesize that an influx of IFNGR-expressing eosinophils responds to CD8-derived IFNG, eliciting signals that then act on esophageal epithelium.

Poster Number 104

Julia Hitschfel, MS
Ragon Institute, Graduate Student | jhitschfel@mgh.harvard.edu

Control of HIV infection in lymph nodes is mediated by cytotoxic CD8 T cells

INVESTIGATORS:B. D. Walker

HIV is a chronic infection that persists latently in lymphoid tissues despite effective antiretroviral treatment (ART). While continuous ART suppresses active viral replication, the latent HIV reservoir is the cause of rapid viral rebound after cessation of treatment, requiring life-long medication for infected individuals. However, a remarkable but small subset of HIV positive individuals exists that can control the infection with their own immune system in the absence of ART. These HIV controllers have exceptionally functional CD8 T cell responses against HIV that are strongly associated with control of the infection. Most studies so far have investigated these CD8 T cell responses in peripheral blood of patients, yet HIV predominately persists and replicates in B cell follicles of lymph nodes that largely exclude and suppress cytotoxic CD8 T cells during homeostasis. Using lymph node biopsies from HIV controllers and ART-suppressed non-controllers, we show that in lymph nodes with high levels of HIV replication there is a local increase in cytotoxic CD8 T cells, including within B cell follicles. We further show that these tissue-derived HIV-specific CD8 T cells from HIV controllers expand and upregulate the cytotoxic molecules Granzyme B and Perforin when stimulated in vitro. However, the ability to expand and upregulate cytolytic effector molecules was strongly reduced in non-controllers, indicating a cytolytic mechanism contains active HIV replication in lymph nodes during spontaneous HIV control.

Poster Number 105

Katrin Sinning, BS
Medicine, Graduate Student | ksinning@mgh.harvard.edu

Dissecting the Role of IgE Glycosylation in IgE-mediated Allergic Responses

INVESTIGATORS: K. Sinning, R. M. Anthony

Immunoglobulin E (IgE) is one of the primary contributors of allergic diseases, which affect 20 % of the population worldwide. IgE's effector functions start by binding to its high-affinity receptor (FcεRI) on mast cells, basophils and eosinophils. Upon antigen stimulation IgE then cross-links to itself, causing degranulation of mast cells, which release inflammatory mediators and initiate allergic cascades. A previous study had identified the oligomannose structure on asparagine-394 (N-394) of human IgE and asparagine-384 of mouse IgE to be both essential and sufficient for IgE responses. This glycan structure consists of up to nine mannoses linked to asparagine over two N-acetylglucosamines. Without this structure, IgE is unable to bind to FcεRI and loses its functional properties. In the current study, IgEs with variable oligomannose structures were generated enzymatically to understand the minimal oligomannose structure essential for IgE integrity and function. We report that IgE with only one N-linked mannose, bound to FcεRI was functionally active. However, an IgE with all mannoses removed, lost binding to FcεRI and was unable to elicit degranulation in-vitro and anaphylaxis in-vivo. Taken together, these results outline the role of N-linked oligomannose structure in regulating IgE functionality and the possible role of specific mannosidases in formulating anti-allergic therapeutics.

Poster Number 106

Maulik Vyas, PhD
Dermatology, Research Fellow | mvyas1@mgh.harvard.edu

Extracellular matrix proteins regulate NK cell function in peripheral tissues

INVESTIGATORS: M. Vyas, M. D. Bunting, M. Requesens, A. Langenbucher, E. B. Schiferle, R. T. Manguso, M. S. Lawrence, S. Demehri

Natural killer (NK) cells belong to the innate lymphoid cell (ILC) family that form a swift acting innate barrier against viral infections and cancer cells. It has long been established in the transplant field that NK cells reject Major Histocompatibility Complex Class I (MHC-I) deficient bone marrow through direct cytotoxicity but tolerate solid organ transplants devoid of MHC-I. In the context of hybrid resistance, parental skin grafts are accepted, but bone marrow cells are rejected by F1 hybrids in an NK cell-dependent manner. Likewise, downregulation of MHC-I is a primary mechanism for immune evasion utilized by solid cancer cells that nonetheless fail to activate NK cells. Elucidating the mechanism that underlies tissue-specific NK cell responses will have major implications in cancer immunology, transplant biology, and virology. Herein, we demonstrate an immediate switch in NK cell function upon exit from the circulation, characterized by a shift from direct cytotoxicity to chemokine/cytokine production. In the F1 skin transplant paradigm, combining an NK cell-specific activating viral ligand, m157, with missing self MHC-I resulted in complete graft rejection, which was dependent on NK cells as potential helpers and T cells as effectors. Extracellular matrix proteins, collagen I, collagen III, and elastin, blocked NK cell cytotoxicity and promoted their chemokine/cytokine production. Importantly, NK cell cytotoxicity against MHC-I-deficient melanoma in the skin was markedly increased using pharmacological inhibitors of tumor collagen deposition. Our findings uncover a fundamental mechanism that restricts direct NK cell cytotoxicity in peripheral tissues and solid cancers.

Poster Number 107

Ana Rita Agra de Almeida Quadros, PhD
Neurology, Research Fellow| ana.quadros@mgh.harvard.edu

Tubulin binding protein Stathmin-2 as a novel pathological hallmark of Alzheimer's disease with TDP-43 pathology

INVESTIGATORS: A. R. Agra de Almeida Quadros, I. S. Ndayambaje, C. Aguilar, H. Stillman, Z. Li, M. Nolan, N. Ramesh, C. Z. Lee, M. Canori, T. Connors, D. Oakley, B. Hyman, S. Das, C. Blackstone, C. Lagier-Tourenne

The discovery of aberrant phosphorylated inclusions of the RNA/DNA binding protein TDP-43 in patients with amyotrophic lateral sclerosis (ALS) and frontotemporal dementia (FTD), significantly changed the field of neurodegeneration. Subsequently, TDP-43 pathology was identified in almost 50% of alzheimer's disease (AD) cases, where it correlates with stronger cognitive decline and smaller hippocampal volume. Even though TDP-43 is recognized as an important pathological hallmark of disease, how TDP-43 leads to neurodegeneration remains largely unknown.

We and others have unveiled loss of stathmin-2 (STMN2) as a pathological hallmark in ALS and FTD. Disruption of TDP-43 function results in misprocessing of STMN2 pre-mRNA, and reduced levels of STMN2 protein. Aberrant truncated STMN2 transcripts were found in postmortem tissues of ALS and FTD patients, where it correlates with phosphorylated TDP-43 levels. STMN2 is a neuronal tubulin binding protein, crucial for axonal growth and regeneration.

We hypothesized that TDP-43 pathology in AD lead to STMN2 misprocessing, impacting axonal integrity and thus neuronal viability. Indeed, we detected abnormal STMN2 RNA in the amygdala of approximately half of AD cases, while none was found in control individuals. We also demonstrated that abnormal STMN2 in AD correlates with phosphorylated TDP-43. To test STMN2 role in axonal integrity, we tested whether tubulin posttranslational modifications were altered in cells with decreased levels of STMN2, and identified a significant decrease in tubulin polyglutamylation and detyrosination, with no change in acetylation. Given the link between axonal health and neurodegeneration, it is critical to further characterize the contribution of this pathway in AD.

Poster Number 108

Corinne Auger, BM
Neurology, Research Technician | caauger@mgh.harvard.edu

Iron deposits, reactive astrocytes, and activated microglia colocalize in cortical tissue with cortical superficial siderosis in cerebral amyloid angiopathy

INVESTIGATORS: M. G. Kozberg, V. Perosa, S. J. Van Veluw, MassGeneral Institute for Neurodegenerative Disease

Cerebral amyloid angiopathy (CAA) is a leading cause of intracerebral hemorrhage (ICH), and cortical superficial siderosis (cSS) has emerged as one of the most important predictors of CAA-related ICH. We hypothesize that local inflammation could drive this association and assessed the distribution of inflammatory markers in relation to cortical iron deposits.

Serial sections from each lobe of nineteen CAA autopsy cases were stained with Perls' Prussian blue (iron) and underwent immunohistochemistry against GFAP (reactive astrocytes) and CD68 (activated microglia). Sections were digitized and uploaded to the cloud-based Aiforia program, where deep-learning algorithms detected tissue, iron, and GFAP- and CD68-positive cells. In MATLAB, serial sections were coregistered, and local densities of iron deposits and inflammatory cells were calculated within all 500μm*500μm squares of cortex and 1000μm-thick consecutive layers in sections with iron density above a predefined threshold.

Locally, the density of iron deposits was positively correlated with GFAP and CD68 density ($p<0.001$, Skillings-Mack), and a stronger local relationship was observed between iron and GFAP. Iron and GFAP densities were highest in the outermost 1000μm layer, compared to deeper layers of the cortex ($p<0.001$, Friedman). CD68 density was high throughout. Iron deposits were seen within reactive astrocytes and activated microglia on double stains.

We show that cSS-induced iron deposition is associated with local inflammation, predominantly in the form of reactive astrocytes but also activated microglia. Both may play a role in secondary tissue injury. Ongoing work examines the spatial extent of the inflammatory response surrounding iron and assesses relationships with neuronal death.

Poster Number 109

Fatemeh Bahari, PhD
Neurology, Research Fellow | fbahari@mgh.harvard.edu

Age-dependent divergence of neuronal response to injury: a mechanistic approach to brain injury in babies

INVESTIGATORS: F. Bahari, K. J. Staley

Brain injury in very low birth-weight (VLBW) babies is extremely common. Intraventricular hemorrhage (IVH) is one of the more severe complications of brain injury in these neonates. In United States alone about 12000 VLBW infants develop IVH every year. A large number of infants with IVH (50% to 75%) later develop cerebral palsy, intellectual disability, and/or hydrocephaly. The pathophysiology of brain injury leading to IVH in this patient population is unclear, therefore providing effective intervention is challenging. We hypothesize that because of the unique salt and water transport systems expressed in immature neurons, unlike mature neurons, they shrink in response to injury. The neuronal volume loss leads to local tissue shrinkage which then triggers blood vessel displacement and rupture, and IVH.
We first clarified the role of salt and water co-transporters in creation of neuronal transmembrane water gradients and ensuing neuronal volume changes by pharmacological or genetic manipulation of the co-transporters activity. We then measured neuronal volume before and after injury. We monitored volume responses in vitro and in vivo using multi-photon imaging of transgenic mice and cellular/molecular techniques.

We found that the injury-induced volume changes were correlated with neuronal age expression levels of salt and water co-transporters: injured immature neurons shrink leading to blood vessel displacement and rupture. Pharmacological alterations in co-transporter activity stabilized the volume response to injury and thus reduced chance of hemorrhage. Our findings can be used to develop new clinical techniques to detect and prevent neuronal shrinkage and the ensuing IVH in VLBW babies.

Poster Number 110

Adel Boudi, PhD
Neurology, Research Fellow | aboudi@mgh.harvard.edu

Assessing somatic instability and neurofilament light chain in biofluids from Huntington's disease models

INVESTIGATORS: A. Boudi, H. Aviolat, B. A. Trombetta, E. Ethier, P. K. Webb, S. E. Arnold, K. B. Kegel-Gleason, M. DiFiglia

Huntington's disease (HD) is a fatal inherited neurodegenerative pathology caused by an expansion of 36 or more CAG nucleotide repeats in the huntingtin gene (HTT). Somatic cells, including neurons in the brain which are particularly vulnerable in HD, present an increase in HTT CAG repeats with age. This phenomenon, called somatic instability, is thought to play a critical role in the onset of the disease.

The detection of HTT CAG expansion is a pertinent lead in the hunt for biomarkers which could provide readouts for diagnostic and drug efficacy evaluation. The current gold standard to identify somatic instability uses a polymerase chain reaction (PCR)based technique to evaluate the number of CAG in HTT gene. Our laboratory has developed an enzyme-linked immunosorbent-based assay (Meso Scale Discovery assay or MSD) that can estimate the average number of glutamines (CAG encodes for glutamine) and therefore use the protein as a readout. Our current work involves expanding the use of this assay in HD mouse models to detect the presence of HTT instability in an easily accessible tissue: the plasma. Additionally, this assay quantifies HTT levels which is relevant to current clinical trials developing HTT lowering strategies. In parallel, we are assessing the presence of neurofilament light chain (NfL), a known biomarker for neurodegeneration, in pre-clinical models of HD using the SIMOA platform.

Poster Number 111

Gracesenia Chahyadinata, BA
Neurology, Research Technician | gchahyadinata@mgh.harvard.edu
Toward Precision Gene Therapy for Treatment of Severe Pain

INVESTIGATORS: A. Battenberg, S. Bazarek, B. Johnston, D. Dubreuil, A. Held, M. Adler, J. Brown, B. Wainger

Chronic pain affects one quarter of adults in the US, a third with impairment of function, and costs over $500 billion annually. Current efforts to treat pain by reducing nociceptor excitability have largely focused on the NaV1.7 channel, since SCN9A (NaV1.7) "knockout" humans have congenital insensitivity to pain. However, strategies to block NaV1.7 voltage-gated sodium channels have had limited success. Furthermore, most pain is focal, whereas almost all treatments are systemic and thus expose patients to potentially unnecessary side effects. We have developed a novel AAV-based approach of potassium channel overexpression that achieves dual spatial and cell-type precision to abrogate pathological pain while minimizing side effects. First, using a generic human synapsin promoter, we show that sciatic nerve injection of a potassium channel yields expression in ipsilateral murine dorsal root ganglia. We validate the analgesic effect of our approach through behavioral experiments: mice injected with AAVs expressing potassium channels exhibit higher mechanical and thermal thresholds; TrpV1::ChR2-EYFP mice, which express the light-sensitive ion channel in nociceptors, injected with these AAVs require higher light intensities to evoke a pain response in optogenetics experiments. To achieve cell-type specificity, we conducted a bioinformatics analysis and identified 13 candidate short promoter sequences (<1kB) that can limit payload overexpression to nociceptors. Preliminary results show robust GFP expression in nociceptors. Taken together, our results validate the overexpression of potassium channels as a promising alternative to NaV1.7 inhibition for pain treatment and support the use of engineered promoters and spatial restriction to achieve precision in AAV-mediated gene therapies.

Poster Number 112

Justine Cohen, PhD
Psychiatry, Research Scientist | justine.cohen@mgh.harvard.edu
Sex Differences in Functional Connectivity during Emotion Regulation and Implications for Healthy Cognitive Aging

INVESTIGATORS: J. E. Cohen, N. E. Fletcher, H. Shields, L. M. Holsen, S. Aroner, H. Aizley, A. Remington, J. M. Goldstein

The ability to regulate emotional response to negative events is critical to mental health and healthy aging. Maladaptive responses to negative stimuli are implicated in Major Depressive Disorder (MDD), a risk factor for cognitive decline. Cognitive reappraisal is one technique used to regulate emotion and involves reframing a situation to change emotional response. In this study we examined sex differences in functional connectivity during an emotion regulation task in participants with or without a history of MDD.

MRI data were collected from 56 adults ages 52-61 with ("cases") and without ("controls") history of MDD. Participants were taught techniques of cognitive reappraisal. In scanner, they were shown negative images and told to either "maintain" or "decrease" their emotional response. Seed-based functional connectivity analyses compared trials between sexes and cases and controls. Results were analyzed in relation to performance on Face-Name associative memory task.

Female controls showed increased connectivity between inhibitory stress regions (HIPP, mPFC) and regions in the DMN (ACC, PCC, precuneus) and prefrontal cognitive control regions (dlPFC, vlPFC) compared to female cases and male controls during the negative decrease condition. Connectivity values in both males and females were strongly correlated with performance on the Face-Name task.

Increased connectivity during emotion regulation is associated with performance on a memory measure used to detect early cognitive changes in aging. Results from this study show that healthy women in midlife are better able to recruit regions involved in cognitive control to attenuate response to negative events and this may be protective during aging.

Poster Number 113

Nikou Louise Damestani, PhD
Radiology, Research Fellow | ndamestani@mgh.harvard.edu

Significant increase of blood transit times with age in female APOE ε4 carriers

INVESTIGATORS: N. L. Damestani, J. Jacoby, R. Almaktoum, A. E. Lovely, M. Eshghi, D. H. Salat, M. R. Juttukonda, Human Connectome Project - Lifespan Consortium

Over 6 million Americans are living with Alzheimer's Disease, with Alzheimer's and dementia-related deaths having increased by 16% during the COVID-19 pandemic. The presence of the apolipoprotein E (APOE) ε4 allele has been identified as the strongest genetic risk factor for Alzheimer's Disease. However, its relationship with underlying biological mechanisms remains unclear. It is also crucial to consider sex-related differences in disease progression. It is well established that female carriers of APOE ε4 present higher risk of neurodegeneration than males, yet this interaction is little understood.

Magnetic resonance imaging (MRI) has localized numerous structural biomarkers for neurodegenerative disorders, furthering our understanding of the aging trajectory. However, such biomarkers often present after substantial neurodegeneration, at which point there are few treatment options. Alternatively, physiological markers typically precede noticeable structural changes. These markers are therefore of great interest for identifying targets for treatment. Perfusion MRI enables probing of measures related to cerebral blood flow, providing specific insight into the evolution of cerebral vasculature. These measures have also been used to predict cognitive decline.

In this study, we used perfusion MRI measures to better understand the interaction of sex and APOE genotype in the aging process. We included a typically aging cohort from the Human Connectome Project – Aging and explored both cortical and subcortical brain regions. We found that women with the APOE ε4 allele demonstrated accelerated increase in blood transit time with age in comparison with men. This could indicate alternative vascular characteristics that are important to explore further.

Poster Number 114

Mark Deehan, PhD
Neurology, Research Fellow | mdeehan@mgh.harvard.edu

Characterization of differentiated human cortical neurons as a model to understand a missense mutation in the gene Nucleus Accumbens 1 that causes a profound developmental delay in humans

INVESTIGATORS: M. Deehan, J. Kothius, E. Weisman, S. Liu, E. Sapp, M. Luliano, C. Seeley, M. Brodsky, M. DiFiglia, K. Kegel-Gleason

In 2017 a de novo point mutation (c. 892C>T, p. R298W) in the gene Nucleus Accumbens 1 (NACC1) was discovered to cause profound neurodevelopmental delay, microcephaly, severe epilepsy, irritability, failure to thrive, and stereotypic hand movements. NACC1 has been previously characterized as a transcriptional repressor in the brain and various cancers yet elucidation of the cellular and molecular functions are poorly characterized. We established embryonic stem cell (ESC) derived human excitatory cortical neurons harboring heterozygote and homozygote R298W mutations. Immunofluorescence revealed that NACC1 is predominantly in the nucleus. Immunofluorescent quantification and western blots analysis revealed that mutant NACC1 accumulates at a higher abundance compared to wildtype. Due to the reported nature of NACC1 acting as a transcriptional repressor, we performed RNA sequencing on NACC1 R298W wildtype and homozygote differentiated cortical neurons to determine pathway level and gene expression changes. Gene Ontology (GO) pathway analysis highlighted synaptic function as positively enriched in R298W homozygotes compared to wildtype neurons. Western blot analysis of Synaptosome associated proteins 25 (SNAP25) and Postsynaptic density protein 95 (PSD95) revealed increased expression in heterozygotes compared to wildtype cortical neurons. Immunofluorescence confirmed an increase in PSD95 but not SNAP25. Fascinatingly, heterozygous NACC1 mutant neurons displayed reduced co-localization of SNAP25/PSD95 implicating a reduction in synaptic formation. Overall, our results highlight that the R298W mutation in NACC1 may cause aberrant synaptic protein expression, formation and function in embryonic stem cell derived cortical neurons.

Poster Number 115

Amanda Duffy, PhD
Neurology, Research Fellow | amduffy@partners.org

Quantifying the number of people who would benefit from an intracortical brain-computer interface

INVESTIGATORS: A. M. Duffy, D. B. Rubin, R. Marujo, D. A. Schoenfeld, L. Chibnik, L. R. Hochberg

Intracortical brain-computer interfaces (iBCIs) have the potential to restore motor function and communication to individuals with neurologic injury and diseases. To quantify those who would or would have benefited from an iBCI for upper extremity use and/or communication within Massachusetts General Hospital Brigham (MGB), we queried the MGB Research Patient Data Registry (RPDR) (data from 6.5 million patients, 2 billion medical records). A team of 8 clinicians and neuroscientists characterized the 132 individuals in RPDR with locked-in state (LIS) into one of eight categories: 1) likely to benefit from an iBCI; 2) unlikely to benefit (due to lack of severity); 3) withdrew life-sustaining therapy; 4) died <1-yr from precipitating event; 5) cognitively impaired/disorder of consciousness; 6) unable to safely undergo iBCI surgery; 7) lacked clinical data; or 8) coding error. Querying 730 other relevant diagnoses yielded >240,000 cases. To characterize these diagnoses, we developed a method to sample a subset of charts to estimate the overall number of people within MGB that would benefit from an iBCI. Diagnoses were clustered by modality (upper extremity/communication) and estimated likelihood of iBCI benefit. Our approach incorporates the variances of these proportions to establish confidence intervals around our estimates. This study characterizes the likelihood of benefit from an iBCI of people diagnosed with LIS within MGB and a methodology to perform an efficient and statistically rigorous review of cases across all relevant diagnoses. Extrapolating results to larger national databases (e.g., private insurance, Medicare) will demonstrate the importance of developing and supporting novel iBCI technologies.

Poster Number 116

Nicole Eklund, BA
Neurology, Clinical Research Coordinator | neklund@mgh.harvard.edu

Home speech and coordination measurement in spinocerebellar ataxias and multiple system atrophy

INVESTIGATORS: N. M. Eklund, J. Ouillon, V. Pandey, A. Pandey, C. D. Stephen, J. D. Schmahmann, K. Z. Gajos, J. Edgerton, A. S. Gupta

Current clinical measures for neurodegenerative diseases are subjective and typically not suitable for frequent at-home administration, resulting in imprecise measurements of disease severity. This study aimed to evaluate the construct validity and test-retest reliability of at-home assessments to monitor disease severity in spinocerebellar ataxias (SCA) and possible/probable Multiple System Atrophy (MSA) patients. Developing accessible tools to measure disease severity will support clinical trials and care for individuals with ataxia.

Subjects participated in a remote study to examine speech, Hevelius computer mouse task performance, and accelerometer data. Participants were mailed a laptop, computer mouse, and 2 GENEActiv devices to wear continuously for one week. To begin, participants underwent a physician-administered examination via Zoom video conference. Following the clinical assessment, participants completed speech surveys and Hevelius computer mouse tasks biweekly for 4 weeks and 5 quality of life and daily function questionnaires at baseline and post-study.

The sample included 22 subjects with SCA/MSA and 7 healthy controls. Analysis of construct validity showed that out of 32 Hevelius features, 15 demonstrated a moderate-strong correlation with remote exam scores (r=0.61-0.81) and 8 demonstrated a moderate-strong correlation with patient reported arm severity scores (r=0.63-0.7). Of those highly correlated features, 13 showed good-excellent test-retest reliability (ICC=0.878-0.985). The assessments demonstrated high feasibility, with 86% of participants fully completing 8 Hevelius sessions.

These data demonstrate the potential use of Hevelius in tracking disease severity in SCA and MSA patients. Our final analysis will include additional modalities, such as data from GENEActiv devices and speech surveys.

Poster Number 117

Paris Fisher, BA
Psychiatry, Clinical Research Coordinator | pifisher@mgh.harvard.edu

Impact of Alzheimer's disease risk factors on memory function and amyloid levels in early midlife

INVESTIGATORS: P. Fisher, K. Konishi, S. Aroner, D. Prokopenko, B. Smith, E. Senko, H. Aizley, A. Remington, A. Touroutoglou, J. Rosand, B. Dickerson, R. Tanzi, J. M. Goldstein

Preclinical risk for Alzheimer's disease (AD), including amyloid (Aβ) deposition, begins 10-15 years prior to AD diagnosis. In addition to genetics, hypertension (HYP), type 2 diabetes (T2D), and major depressive disorder (MDD) in midlife are major risk factors for AD. We hypothesize that in midlife, these risk factors will be related to poor cognitive performance and increased Aβ deposition, prior to the onset of overt clinical symptoms. Cognitive function was assessed in high- (HR) and low-risk (LR) subjects (N=83; ages 50-70 yrs) using the Face-Name Associative Memory Test (FN), 6-Trial Selective Reminding Test (SRT), Verbal Fluency Task (FAS/CAT), and Digit Span (DS). Aβ was detected through PET using C-11PiB. Here we show that HR, defined as those with genetic risk plus HYP, T2D, and/or MDD, is associated with lower cognitive performance (FN: $F=14.30$, $p<0.001$; CAT: $F=7.02$, $p<0.01$; DS: $F=4.65$, $p<0.03$) and higher Aβ deposition ($F=4.01$, $p<0.05$). In midlife, genetic risk plus poor cardiometabolic health was associated with lower memory performance across all cognitive domains (HYP: FN: $F=11.75$, $p<0.01$; SRT: $F=5.04$, $p<0.05$; CAT: $F=8.14$, $p<0.01$; DS: $F=7.73$, $p<0.01$; T2D: FN: $F=8.57$, $p<0.01$; SRT: $F=5.26$, $p<0.05$; CAT: $F=7.77$, $p<0.01$; DS: $F=6.38$, $p=0.01$), while the impact of MDD was limited to associative memory (FN: $F=4.29$, $p<0.05$). These results suggest that genetic and clinical risk factors for AD may help identify early targets for intervention in those at risk of AD later in life.

Poster Number 118

Jessie Fang-Lu Fu, PhD
Radiology, Research Fellow | flfu@mgh.harvard.edu

Examining kinetic spectrum of extracerebral signal and its contributions to reference regions of 18F-MK6240 PET

INVESTIGATORS: J. F. Fu, C. Lois, J. Sanchez, J. A. Becker, Z. B. Rubinstein, E. Thibault, A. N. Salvatore, H. Sari, M. E. Farrell, M. Normandin, N. Guehl, G. El Fakhri, K. A. Johnson, J. C. Price

Introduction: Off-target 18F-MK-6240 binding to melanocytes (extracerebral signal (EC)) can contaminate cerebellar gray matter (CerGM) reference uptake and impact the detection of emergent tau signal in Alzheimer's disease (AD). We compared 18F-MK6240 kinetic spectra quantified in EC, CerGM and alternative reference regions to inform reference region selection, across the AD spectrum.

Methods: Thirteen subjects (8 controls (CN)–63±12yrs; 5 mild cognitive impairment (MCI) or AD–75±9yrs) underwent 120 min 18F-MK6240 PET, MRI, and arterial blood sampling. Masks for EC and reference regions (CerGM, eroded CerGM 3mm, inferior CerGM (InfCer), cerebral white matter (WM) and pons) were generated. Spectral analysis (SA) was applied to decompose 18F-MK6240 uptake into spectral components with frequency beta and amplitude alpha. SA kinetic spectra were compared between EC and reference regions.

Results: SA indicated 2 reversible components in reference regions: 1) beta~0.03min-1 (slow, non-displaceable uptake), 2) beta~0.18min-1 (fast, tracer delivery). Compared to CerGM, EC SUV was 30% higher and constantly increasing in late frames and only exhibited a fast component with 90% lower amplitudes ($P<10E-5$). A trapping/irreversible component (beta =10E-5min-1) was detected in all regions, with amplitudes significantly higher in EC (3-fold) than in other regions ($P<0.05$). Compared to CerGM, trapping amplitudes were higher in InfCer, but lower for WM, pons and eroded CerGM.

Conclusion: SA supports a 2-tissue compartment configuration in reference regions. EC signal uniquely exhibited 1 reversible component and largest trapping amplitudes. The trapping component in reference regions likely reflects EC contamination, which was most evident in InfCer and less prevalent in WM and pons.

Poster Number 119

Juliana Ison, BA
Neurology, Research Technician | jison1@mgh.harvard.edu

Assessing Barriers to Research for an Online Study of Parkinson's Disease

INVESTIGATORS: J. M. Ison, A. V. Sanchez, H. Hemley, J. D. Jackson

Despite federal regulations which mandate the inclusion of underrepresented groups (e.g., racial and ethnic minority populations, rural populations, low-income populations, populations with low educational attainment) in research, the involvement and systematic inclusion of these communities in clinical investigation remains disproportionately low. Although researchers have surveyed and speculated on barriers to clinical research, few studies have measured access to clinical investigation in real time. Hence, for the Fostering Inclusivity in Research Engagement for Underrepresented Populations in Parkinson's Disease (FIRE-UP PD) Study—a multi-site online study funded by the Michael J. Fox Foundation—investigators created a dashboard of commonly-cited barriers to research participation. Barriers tracked included those related to language needs, digital limitations, trust, time commitment, transportation, contact information, and privacy concerns, and participants were able to describe other limitations not captured under the aforementioned categories. While 295 participants were recruited to the FIRE-UP PD Study, the barriers dashboard captured an additional 230 potential participants who expressed interest in participating but were otherwise unable due to the tracked barriers. Of the reported barriers, language needs and the digital divide (i.e., lack of access to internet, email, digital device, etc.) were the most frequently reported. Interestingly, lack of trust, a barrier commonly invoked by researchers to account for low participation among racial and ethnic minorities, was not frequently endorsed by prospective participants. Better understanding barriers to research for prospective participants will allow researchers to more aptly address these in the future investigation and in turn foster more equitable research recruitment practices.

Poster Number 120

John Jacoby, BS
Radiology, Research Technician | jjacoby@mgh.harvard.edu

Measuring regional effects of demographic factors on cortical hemodynamics

INVESTIGATORS: N. L. Damestani, D. H. Salat, M. R. Juttukonda

Alzheimer's Disease (AD) cost the United States an estimated $305 billion in 2020, with costs expected to increase to over $1 trillion each year by 2050. Characteristics of blood flow throughout the brain are known to be correlated with measures of cognitive health and clinical function in AD. However, the reasons for these relationships have yet to be fully explained. Understanding how blood flow changes with demographic group in healthy adults could provide context for understanding hemodynamic pathology in AD patients.

Magnetic resonance imaging (MRI) has been a vital tool for exploring the disease progression of Alzheimer's and other forms of dementia. Perfusion MRI is a technique that allows for noninvasive analysis of blood flow throughout the brain. This data is frequently analyzed with region of interest (ROI)-based approaches in the brain. However, this approach could mask higher-resolution spatial effects. An alternative is surface-based cortical analysis, which allows for effects to be analyzed at each location in the cerebral cortex.

Here, we used perfusion MRI and cortical surface-based analyses to characterize the effects of age and sex on blood flow and blood transit time in the Human Connectome Project – Aging cohort. We found that older individuals have decreased blood flow and increased transit time compared to younger individuals. In addition, we found that women have increased blood flow and decreased transit time compared to men. Finally, we found that blood flow decreased more slowly with age in men than women in certain brain regions but not in others.

Poster Number 121

Sophia Keins, BS
Neurology, Research Technician | skeins@mgh.harvard.edu

Social Determinants of Depression Incidence After Intracerebral Hemorrhage

INVESTIGATORS: J. R. Abramson BA, A. Mallick MD, A. Ganbold BS MS, C. Kourkoulis BS, M. E. Gurol MD MSc, S. M. Greenberg MD PhD, C. D. Anderson MD MMSc, J. Rosand MD MSc, A. Viswanathan MD PhD, H. Alabsi DO, A. Biffi MD

Background: Over 30% of Intracerebral Hemorrhage (ICH) survivors develop depression post-stroke. No studies have examined the relationship of social determinants of health (SDOH) with neuropsychiatric outcomes following ICH. We hypothesized that pre-hemorrhage SDOH are crucial risk factors for post-ICH depression. We investigated structural (community-level) and individual-level SDOH as determinants of new-onset depression after ICH.

Methods: We analyzed data from ICH survivors presenting at MGH between 2006 and 2017. We collected information from electronic health records (EHR), follow-up interviews, and neuroimaging. Participants' counties of residence were used to incorporate structural SDOH including air quality, social vulnerability, education, access to food, and socio-economic status.

Results: Among 610 participants, average age was 70.9, 322 (52.7%) were male, and 489 (80.2%) self-reported White race/ethnicity. Single marital status (OR 0.52, 95% CI 0.31-0.86) and county poverty level (OR 1.04 per percent, 95% CI 1.00-1.08) were associated with post-ICH depression, after adjustment for established biological predictors. We also found that Asian participants with lobar ICH were more likely to experience new depression after hemorrhagic stroke when compared with White participants (interaction $p<0.05$).

Conclusions: Here we show that SDOH, including structural SDOH, are associated with new onset depression following ICH. Of note, structural-level poverty rates were found to be novel risk factors for depression among ICH survivors, with likely crucial implication for both patient care and public health policy. Asian ICH survivors with lobar hemorrhage may be at higher risk of post stroke depression than their White counterparts.

Poster Number 122

Patricia Kelly, PhD
Neurology, Research Fellow | hpkelly@mgh.harvard.edu

A preclinical model to prevent the adverse events of Amyloid Related Imaging Abnormalities (ARIA) during Aduhelm treatment in patients with Alzheimer's disease

INVESTIGATORS: P. Kelly, S. Whiteman, A. Scherlek , S. S. Hou, T. Bussière, B. J. Bacskai

Amyloid-Related Imaging Abnormalities (ARIA) represent a spectrum of radiographic abnormalities first observed in the brain of participants with Alzheimer's disease (AD) during the clinical testing of anti-amyloid antibody treatment. Integrated safety data from the phase 3 clinical testing of Aduhelm showed 40% participants developed ARIA, one quarter developed symptoms (confusion and/or dizziness) and 1.4% experienced serious ARIA symptoms requiring hospitalization. The recent FDA approval of Aduhelm will for the first time move ARIA detection and management into the clinic. We tested our hypothesis that ARIA formation can be studied by longitudinal in vivo multiphoton imaging within the brain of awake APP/PS1 mice (a transgenic mouse model of AD) during chronic treatment with either aducanumab (Aduhelm), mE8 (Donanemab) or 3D6 (Bapineuzumab). Similar to findings of the clinical testing of Aduhelm, Donanemab and Bapineuzumab in AD patients, we observed ARIA as an early event in APP/PS1 mice during 3D6 treatment. We observed the erosion of individual amyloid plaques and increased vascular permeability as an early event in the formation of hemorrhagic ARIA followed by a breakdown of the blood-brain barrier (BBB), a loss of vascular amyloid from CAA-positive vessels and a rapid vascular structural deterioration in 3D6-treated mice. The pathological vascular extravasation in vivo was observed as Prussian blue-positive hemorrhagic iron staining in brain sections from 3D6-treated APP/PS1 mice. Here we show the in vivo trajectory of ARIA-related hemorrhage formation involving amyloid plaques and CAA in the awake mouse brain. Our preclinical ARIA model will catalyze our understanding of ARIA towards prevention.

Poster Number 123

Paulina Knight, BA
Radiology, Clinical Research Coordinator | pcknight@mgh.harvard.edu

Neuroinflammation and reduced neural integrity in chronic low back pain: a magnetic resonance spectroscopy study

INVESTIGATORS: P. C. Knight, A. Weerasekera, Z. Alshelh, E. J. Morrissey, A. Saha, M. Kim, Y. Zhang, V. Napadow, A. Torrado-Carvajal, R. R. Edwards, E. M. Ratai, M. L. Loggia

A previous study by our group showed that knee osteoarthritis (KOA) patients demonstrate alterations in thalamic levels of several metabolites, as measured by 1H-magnetic resonance spectroscopy: i.e., higher myo-inositol (mIns), lower N-acetylaspartate (NAA) and lower Choline (Cho), compared to healthy controls. We sought to replicate these results in a different musculoskeletal pain condition, chronic low back pain (cLBP), and explore whether these metabolites would resolve clinical subtypes of cLBP. Twenty-nine cLBP patients (twenty-two with axial low back pain, cLBPAX, and seven with radicular low back pain, cLBPRAD), and twenty healthy controls were scanned using a conventional PRESS sequence (TE=30ms; TR=1.7s; voxel size=15x15x15mm) with voxel placement in the left thalamus. Using water-normalized levels, cLBP patients demonstrated higher mIns ($p<0.01$), lower NAA ($p<0.001$) and lower Cho ($p<0.05$) than healthy controls, replicating our prior KOA results in this cLBP cohort. Additionally, NAA was reduced in cLBPAX when compared to cLBPRAD ($p<0.05$), whereas differences found in Cho and mIns were not statistically significant ($p<0.20$ and $p<0.15$, respectively). While pain severity scores were not correlated with metabolite levels, the degree of nociplastic pain, as measured by score on the American College of Rheumatology Fibromyalgia Survey, negatively correlated with NAA. These results suggest that thalamic metabolite changes may be common across spatially different musculoskeletal chronic pain conditions for mIns, a marker of glial dysfunction, NAA, a marker of neuronal integrity, and Cho, a membrane turnover marker. Additionally, the differences between cLBP subtypes suggest that neuronal integrity may play a role in the pathophysiology of nociplastic pain.

Poster Number 124

Hoang Le, PhD
Neurology, Research Fellow | hle306@mgh.harvard.edu

The gain-of-function T96K Mutation in TREM2 Leads to Decrease Microglial Activation in Alzheimer's Disease

INVESTIGATORS: H. Le, L. Quinti, W. Eimer, S. Heitman, D. McGinty, K. Flynn, A. Griciuc, R. Tanzi, Cure Alzheimer's Fund; NIH/NIA

Alzheimer's disease (AD) is a debilitating neurodegenerative disorder and the leading cause of dementia. However, the molecular mechanisms underlying AD remain largely unknown. Genome-wide association studies (GWAS) have identified many AD risk genes related to innate immune response and microglia. Among those genes is the triggering receptor expressed on myeloid cells 2 (TREM2), which is specifically expressed in microglia. We previously reported that the T96K mutation in the ligand-binding domain of TREM2 is associated with increased AD risk. We showed that this variant led to enhanced binding to TREM2 ligands, suggesting TREM2T96K is a gain-of-function mutation in AD. While TREM2 loss-of-function mutations have been extensively investigated, no studies yet have been reported showing the effects of TREM2 gain-of-function mutations in mouse models of AD. We recently generated the Trem2T96K knock-in (KI) mouse model that carries the T96K mutation using CRISPR/cas9 gene editing and crossed them to the 5×FAD mouse model of AD. Remarkably, we found that Trem2T96K mutation led to increased levels of insoluble amyloid beta (Aβ)42 in female 5×FAD mice. Trem2T96K mutation resulted in reduced microglia numbers and clustering of microglia around Aβ plaques in female 5×FAD mice. Trem2T96K mutation also led to decreased levels of soluble (s) Trem2 in 5×FAD mice and cell surface expression of TREM2 on microglial cells. Moreover, Trem2T96K mutation resulted in reduced phagocytosis of Aβ42 in microglial cells. Our findings provide critical insight into the role of TREM2T96K mutation in modulating microglial pathology in AD and may contribute to AD drug discovery and development.

Poster Number 125

Jea Hwang Lee, PhD
Center for Genomic Medicine, Research Fellow | JLEE252@mgh.harvard.edu

Difference Ile219 between Val219 on MLH1 protein stability through p97/VCP-mediated ubiquitination relates with CAG instability in Huntington disease

INVESTIGATORS: J. Lee, J. Ruliera, B. Shin, I. Seong, V. C. Wheeler

Genome-wide association studies have identified MLH1 as a modifier of the age of onset of Huntington's disease (HD) that is caused by inheriting an expanded CAG repeat in the HTT gene. MLH1 encodes a mismatch repair protein essential for the further expansion of the CAG repeat in somatic cells. In humans, the likely functional MLH1 SNP underlying disease modification specifies an Ile>Val substitution at amino acid 219 (I219V). Understanding the consequences of this variant in patient cells provides a critical route to delineating HD-relevant mechanisms that could be targeted to alter the disease course. Here, we have employed HD patient and control lymphoblastoid cell lines (LCLs) harboring MLH1 modifier allele(s) to explore the impact of the I219V variant. Using mass spectrometry (MS) assays specifically targeting either MLH1-I219 or MLH1-V219 we show that MLH1-V219 is turned over at a higher rate than MLH1-I219, and to a greater extent in HD than control LCLs. We also find that ubiquitin co-immunoprecipitates (IPs) with MLH1 in a manner that depends on the number of V219-expressing alleles. To examine mechanisms of protein turnover we investigated VCP (p97) that segregates proteins from complexes, membranes and chromatin to facilitate their degradation. Interestingly, using both immunoblot and MS-based analyses we find that VCP preferentially co-IPs with MLH1-V219 in HD LCLs. Together, these findings suggest that I219V impacts MLH1 stability via its interaction with VCP and indicate that HD cells provide a background on which effects of this variant can be revealed and harnessed for potential therapeutic strategies.therapeutic target for preventing the corneal stromal complications of EKC.

Poster Number 126

Jian Li, PhD
Radiology, Research Fellow | jli112@mgh.harvard.edu

Translation of the subcortical functional connectivity mapping from 7T to 3T

INVESTIGATORS: J. Li, M. K. Cambareri, B. Guerin, D. D. Dougherty, A. V. Dalca, B. Fischl, A. Horn, B. L. Edlow, Tiny Blue Dot Consciousness Consortium

For patients with disorders of consciousness (DoC), functional connectivity analysis is a widely used approach to identify subcortical network hubs that could be used as therapeutic targets for neuromodulation. Although the optimal therapeutic targets have not been well defined, the default mode network (DMN) is well established as a network that contributes to the modulation of consciousness. We recently mapped the subcortical connectivity of the DMN using 7T resting-state fMRI (rs-fMRI) data from the Human Connectome Project (HCP). Here, our aim is to determine whether this subcortical DMN map can be reproduced in data with lower signal to noise ratio (SNR). We used 1,000 healthy subjects with 3T rs-fMRI scans also from the HCP dataset. We applied the group BrainSync+NASCAR tensor decomposition pipeline to the rs-fMRI data and the DMN was identified from the decomposition result. To explore the sample size effect and the potential subject selection bias, we performed the same pipeline on the same group of 84 subjects as used in the previous 7T analysis as well as on a group of randomly selected 86 subjects who did not participate in any 7T scan. We found that the subcortical DMN functional connectivity can be reproduced from 3T healthy control data. However, this reproducibility requires a substantially larger dataset than that used in the 7T study to compensate for the lower SNR in the 3T scans. These findings suggest that clinical translation of the subcortical DMN functional connectivity to individual patients will require development of novel methods.

Poster Number 127

Su Min Lim, PhD
Neurology, Research Fellow | slim13@mgh.harvard.edu
Optical pooled screens for regulators of FUS localizationOptical pooled screens for regulators of FUS localization

INVESTIGATORS: S. Lim, J. Qiu, N. Mishra, M. Kwon, M. Canori, F. Freyermuth, Y. Han, C. Lee, C. Aguilar, P. Van Damme, P. Rogers, A. Held, B. Wainger, J. Doench, A. Singh, P. Blainey, C. Lagier-Tourenne

Protein mislocalization and aggregation are hallmarks of several neurodegenerative disorders. The RNA-binding protein FUS plays a major role in RNA metabolism and is found to be mutated and/or mislocalized to the cytoplasm in amyotrophic lateral sclerosis (ALS) and frontotemporal dementia (FTD). Indeed, FUS, a predominantly nuclear protein, abnormally accumulates in the cytoplasm upon cellular stress and when mutated, but the underlying cellular mechanisms remain unclear. Our project aims to identify regulators of FUS mislocalization and factors mediating aberrant stress granule assembly/disassembly by performing optical pooled screens in skin fibroblasts, ReNcell VM immortalized human neural cells, and iPSC-derived neurons from ALS patients. Optical pooled screen is a novel approach for large genomic screens that has shown tremendous potential to uncover disease mechanisms in cancer cells but has not yet been used in neurodegenerative diseases. Using targeted in-situ sequencing to provide massively scalable integration of barcoded pooled CRISPR sgRNAs libraries, we connect genetic perturbations with high-content image-based phenotypes of FUS and stress granules at single-cell resolution. Our pilot screen (167 genes, 668 sgRNAs) in patient fibroblasts identified novel targets that exacerbate or restore abnormal accumulation of cytoplasmic FUS. In addition, we successfully performed in situ sequencing in ReNcell VM human neurons and iPSC-derived neurons from ALS patients, which establishes for the first time the feasibility of optical pooled screens in human neurons. Undertaking a large-scale optical screen in fibroblasts and neurons from patients with FUS mutations has the potential to identify new therapeutic targets for ALS/FTD.

Poster Number 128

Anna Luddy, BS
Neurology, Clinical Research Coordinator | aluddy1@mgh.harvard.edu
Free-living motor activity measurements in ataxia-telangiectasia

INVESTIGATORS: A. C. Luddy, N. C. Khan, J. Thornton, S. Reiling, A. S. Gupta

Background: As disease therapies for ataxias are investigated, it is necessary to develop free-living motor biomarkers to evaluate disease severity and progression. Caregiver reported outcome measures (CROMs) also supply information about disease severity that are not captured by other assessments. This study sought to test the hypothesis that metrics derived from a wrist worn accelerometer and CROMs can provide accurate and reliable information about disease severity.

Methods: Data were collected remotely from 31 participants with ataxia-telangiectasia (A-T) and 27 control participants ranging from two to nineteen years of age. 14 participants with A-T and 13 controls completed the study at two time points separated by one year. Participants were asked to wear a GENEActiv accelerometer on their dominant wrist continuously for one week. They also completed a speech survey three times over the week. Following the study caregivers also filled out CROMs including the CPCHILD and Dysarthria Impact Scale.
Results: Features extracted from passive wrist sensor data were highly informative for distinguishing individuals with A-T from healthy controls, and correlated strongly with the Brief Ataxia Rating Scale, a motor subset of CPCHILD, and neurofilament light chain concentration. Several wrist sensor features captured disease progression over a 1-year interval.

Discussion: These results demonstrate that data from wrist sensors produce reliable and informative measures of motor function and may be useful as an outcome measure for monitoring disease. We plan to extend data collection over a period of two years to better characterize the longitudinal properties of wrist sensor features.

Poster Number 129

Brenna McKaig, BS
Emergency Medicine, Clinical Research Coordinator | bmckaig@mgh.harvard.edu
Feasibility of Portable Magnetic Resonance Imaging in the Emergency Department

INVESTIGATORS: R. Schleicher, K. Dickerson Mayes, MD, PhD, B. Alden Parry, C. Beakes, J. Margolin, E. Kugener, R. Mayper, C. Wira, MD, K. Sheth, MD, W. T. Kimberly, MD, PhD, J. N. Goldstein, MD, PhD

Background: Magnetic resonance imaging (MRI) is an important tool for assessing neurologic emergencies in the emergency department (ED). Current MRI technology can be time-consuming and difficult to obtain for critically ill patients. Portable MRI technology may offer a point-of-care option at a lower cost and better feasibility.

Methods: We performed a single center pilot study in the MGH ED. This study employed a Hyperfine MRI system, operating at 0.064T magnetic field strength, and performed DWI, T2, T1, and FLAIR imaging of the brain. Trained clinical research staff approached a convenience sample of patients undergoing brain imaging as standard of care for any neurologic indication.

Results: Over 9 months, 18 patients were enrolled and 17 completed imaging. One patient was excluded from imaging due to a contraindication to MRI identified during MRI safety screening. 14 patients underwent MRI in their patient rooms while they remained on central telemetry. 3 patients in the waiting room or sitting in chairs underwent MRI in a nearby phlebotomy room. Scan time was on average 41 +/- 3 minutes, with a median of 42 minutes. Challenges included navigating the portable MRI through narrow hallways crowded with patients in stretchers; bays with multiple patients; and finding an appropriate storage location for the Hyperfine MRI system with both power and an ethernet connection.

Conclusions: Portable MRI is a feasible option for neuroimaging in the ED.

Poster Number 130

Noya Meital-Kfir, PhD
Neurosurgery, Research Fellow | nmeital-kfir@mgh.harvard.edu
Simulating the effect of asynchronous phosphene stimulation on artificial vision

INVESTIGATORS: N. Meital-Kfir, J. S. Pezaris

Electrical micro-stimulation techniques used in visual prostheses are designed to restore visual functions following acquired blindness. Induced focal percepts, known as phosphenes, are achieved by applying localized electrical pulses to the visual pathway to bypass the impaired site. A complex artificial percept is achieved by coordinated electrical stimulation across multiple electrodes generating patterns of phosphenes corresponding to the external world. Here, we explore the temporal relationships between individual phosphenes on object binding and perception. We hypothesize that synchronous phosphene presentation will facilitate object perception as compared to asynchronous presentation.

A model system with sighted subjects, using virtual reality technologies, was used to simulate prosthetic vision. Subjects completed a simple sentence reading task, based on the MNREAD test of visual acuity, at varying font sizes (1.1-1.4 logMAR) and under varying levels of phosphene temporal noise. The results indicate high sensitivity to even short latencies between the current eye position and phosphene update, with reading performance dropping off significantly with increasing latency. Reading performance was also significantly affected by temporal noise in phosphene presentation, with increasing desynchronization driving lower reading scores. We conclude that object perception (here, text perception) is enhanced with synchronously presented phosphenes as compared to asynchronously presented ones. These results are fundamental for developing an efficient temporal pattern of stimulation and for the creation of functional prosthetic vision.

Poster Number 131

Alan Mejia Maza, PhD
Center for Genomic Medicine, Research Fellow | amejiamaza@mgh.harvard.edu

Tissue-specific and repeat length-dependent somatic instability of the X-linked dystonia parkinsonism-associated CCCTCT repeat

INVESTIGATORS: L. N. Campion, A. J. Mejia Maza, R. Yadav, E. B. Penney, M. G. Murcar, K. Correia, T. Gillis, C. Fernandez-cerado, S. Velasco-Andrada, G. P. Legarda, N. G. Ganza-Bautista, J. B. Lagarde, P. Acuña, G. Multhaupt-Buell, G. Aldykiewicz, M. L. Supnet, J. K. De Guzman, C. Go, N. Sharma, E. L. Munoz, M. C. Ang, C. Czarina, E. Diesta, D. C. Bragg, L. J. Ozelius, V. C. Wheeler, The Collaborative Center for XDP

The insertion of a SINE-VNTR-Alu (SVA) retrotransposon in the TAF1 gene causes X-linked dystonia parkinsonism (XDP), an adult-onset neurodegenerative disease endemic to the Philippines. The SVA contains a polymorphic CCCTCT motif, whose length is inversely correlated with disease onset, placing XDP in a class of repeat expansion disorders and motivating investigation of CCCTCT repeat instability in brain tissues. Here, we quantified somatic instability in blood and in up to 17 brain regions across 41 XDP male individuals. We detect repeat length-dependent and tissue-specific somatic CCCTCT repeat expansion, with brain showing greater levels of expansion than blood. The brain exhibits region-specific patterns of instability that are similar across individuals, with cerebellum exhibiting low instability and cortex exhibiting relatively high instability. The spectrum of somatic instability includes a high proportion of moderate repeat length changes of up to 5 repeats, as well as expansions of ~20->100 repeats and contractions of ~20-40 repeats at lower frequencies. Comparison with HTT CAG repeat instability in postmortem Huntington's disease brains reveals similar brain region-specific profiles, indicating common factors contributing to the instability of both repeats. Analyses in XDP brains of a non-disease-associated SVA CCCTCT repeat in the LIPG gene, reveals repeat length-dependent expansion at overall lower levels relative to the XDP CCCTCT repeat, suggesting that expansion propensity may be modified by local chromatin structure. Together, the data support a role for repeat length-dependent somatic expansion in the process(es) driving the onset of XDP and prompt further investigation into repeat dynamics and the relationship to disease. PUIs and safe discontinuation of precautions.

Poster Number 132

Negar Molazadeh, MD
Neurology, Research Fellow | nmolazadeh@mgh.harvard.edu

Progression independent of relapse activity (PIRA) in neuromyelitis optica spectrum disorder (NMOSD) and myelin oligodendrocyte glycoprotein (MOG) antibody disease

INVESTIGATORS: N. Molazadeh, M. Levy

Progression independent of relapse activity (PIRA) is referred to a neurologic progression outside of relapses, or an ongoing disability worsening in a period between relapses in Multiple Sclerosis (MS), a known inflammatory demyelinating disease of the central nervous system. Although PIRA is well investigated in MS, it has not been detected in neuromyelitis optica spectrum disorder (NMOSD) and myelin oligodendrocyte glycoprotein antibody disease (MOGAD). Here we aim to determine if PIRA is detectable in a large cohort of immunologically stable NMOSD and MOGAD patients. In this retrospective multi-center study, we will review medical records of NMOSD, MOGAD and matched MS patients using datasets of Massachusetts General Hospital and the Guthy Jackson Charitable Foundation CIRCLES international registry from 2010 - 2020. To maximize detection of all worsening events (i.e. PIRA) we will compare roving Expanded Disability Status Scale (EDSS) scores to final EDSS scores in subjects with NMO/MOG who are in immunological remission throughout the study period. Then we will identify associations in NMOSD patients with evidence of PIRA, in regard to demographic, serological, clinical, radiological and OCT and VEP findings and compare them with MS patients as our control group. The findings of this study may confirm or challenge the current view of the natural history of NMOSD and MOGAD and may suggest new treatment and monitoring targets to achieve maximal control of disease progression and may guide to design a prospective data collection study to look for evidence of PIRA from the initial diagnosis time.

Poster Number 133

Leon Munting, PhD
Neurology, Research Fellow | lmunting@mgh.harvard.edu

Impaired cerebral blood flow and cerebrovascular reactivity in the APP23 mouse model of cerebral amyloidosis

INVESTIGATORS: L. P. Munting, M. G. Kozberg, L. Hirschler, J. Warnking, E. L. Barbier, A. Van der Kouwe, J. B. Mandeville, C. T. Farrar, S. M. Greenberg, B. J. Bacskai, S. J. Van Veluw

Background: In patients with cerebral amyloid angiopathy (CAA), amyloid-beta deposits in the walls of brain arteries and arterioles, ultimately leading to stroke and dementia. Impaired cerebrovascular reactivity (CVR) is an early symptom of CAA (PMID: 31827267). The APP23 mouse model develops similar amyloid-beta deposits and develops microbleeds and reduced cerebral blood flow (CBF) (PMID: 25384087). It is however still unclear if the model has similar CVR impairments, and if there is a spatiotemporal association between microbleeds and cerebrovascular function.

Aim: To measure CBF, CVR and microbleeds with MRI in APP23 mice.

Method: APP23 mice and age-matched wild-types (WT) were scanned with a 9.4T MRI scanner under 1.1% isoflurane at 12, 18 and 24 months (n=5-8 in each group). A 15-minute pseudo-Continuous Arterial Spin Labeling (pCASL)-MRI sequence was used to measure CBF, while 10% CO2 was administered from minute 10-15. CVR was defined as the percentage CBF increase during CO2-administration. A multi-gradient echo (MGE) sequence was used to detect microbleeds.

Results/Conclusions: CBF and CVR were significantly reduced in 24-month-old APP23 mice ($p<0.001$ & $p=0.04$ respectively). A median of 9 microbleeds were found in this cohort, which significantly correlated with CBF ($p=0.01$) but not CVR ($p=0.71$). In the 18-month-old cohort, only CBF was significantly reduced ($p<0.01$), but not CVR ($p=0.69$), while in the 12-month-old cohort, no differences were found. The non-invasiveness of this study, combined with the clinically relevant manifestations of CAA in APP23 mice, enable to test the effect of potential new treatments on cerebrovascular function in the context of CAA.

Poster Number 134

Matthew Nolan, PhD
Neurology, Research Fellow | matthew.nolan@mgh.harvard.edu

Inhibition of the HMG-CoA reductase-mediated mevalonate pathway increases STMN2 expression in TDP-43-deficient neurons

INVESTIGATORS: M. Nolan, S. Ndayambaje, A. Rita Agra De Almeida Quadros, C. Z. Lee, C. Aguilar, W. C. Huang, M. Adler, A. Held, J. Smith, M. Canori, Z. Melamed, M. Baughn, D. Cleveland, C. Lagier-Tourenne

Amyotrophic lateral sclerosis (ALS) and Frontotemporal Dementia (FTD) are devastating neurodegenerative diseases for which no disease-modifying treatments are available. Both diseases are associated in a majority of cases with the nuclear clearance and cytoplasmic aggregation of the RNA-binding protein TDP-43 in neurons and glia at post-mortem. Loss-of-nuclear TDP-43 function results in the mis-splicing of a cryptic exon within the first intron of the critical neuronal microtubule-associated protein stathmin-2 (STMN2), and a subsequent reduction in its expression. Previous work has demonstrated the utility of rescuing STMN2 levels in TDP-43 deficient neurons, highlighting it as a promising therapeutic target in ALS/FTD. Using CRISPR-Cas9 editing, we generated new cellular models for high-throughput monitoring of endogenous stathmin-2 levels in TDP-43-deficient cells. Screening of 11,895 unique compounds identified cholesterol lowering statins as potent mediators of STMN2 at both the RNA and protein levels. siRNA knockdown of the gene encoding HMG-CoA (HMGCR) and concomitant statin/mevalonate treatment confirmed the involvement of the cholesterol synthesis pathway. Lovastatin and Simvastatin repress this pathway to decrease cholesterol synthesis via inhibition of HMG-CoA reductase and are both FDA-approved and blood-brain barrier penetrant. Here we identify - for the first time - the rescue of neuronal STMN2 via inhibition of HMG-CoA reductase, and link neurite outgrowth potential with cholesterol metabolism. These results may be of translational importance in ALS/FTD.

Poster Number 135

Sara Romanella, MS
Radiology, Graduate Student | sromanella@mgh.harvard.edu

Adapting Transcranial Magnetic Stimulation to Spaceflight-Induced Brain Changes

INVESTIGATORS: S. M. Romanella, L. Mencarelli , K. Seyedmadani , S. Jillings , E. Tomilovskaya , I. Rukavishnikov , G. Sprugnoli , S. Rossi , F. Wuyts , E. Santarnecchi

As space agencies prepare for longer deep-space missions, astronauts' health has become an impelling concern. Transcranial magnetic stimulation (TMS) could be implemented as countermeasure to brain health risks. Potential applications include pre-flight training and optimization of crew performance. We investigated how to optimize TMS for structural brain changes associated with long-duration spaceflight.

We collected magnetic resonance imaging (MRI) scans from 14 non-flyers controls and 15 astronauts/cosmonauts before and after 6 months on the International Space Station, and 7 months after re-entry. We used biophysical modeling to segment the anatomical images and create individual 3D meshes. We simulated the electrical field generated by TMS over cortical areas associated with cognitive and visuomotor functions relevant for space operations and analyzed changes in total cerebrospinal fluid volume (CSF).

After spaceflight, astronauts presented an increase in CSF volume ($p=0.0005$), which was correlated with changes in the amount of electrical stimulation generated in the brain by TMS. Moreover, post-mission, astronauts exhibited a significant decrease of induced stimulation over left angular gyrus ($p=0.003$) and an increase over left primary motor cortex ($p=0.048$), compared to controls. Data suggest that these changes may be caused by structural brain modifications, such as an upward shifting of the brain as documented in prior studies.

We were able to optimize intensity, position, and orientation of TMS coil by taking into account individual variability in brain anatomy and spaceflight-associated brain changes. Once optimized, noninvasive brain stimulation techniques (NIBS), such as TMS, could constitute a valuable approach to promote brain health in space.

Poster Number 136

Zahra Shirzadi, PhD
Neurology, Research Fellow | zshirzadi@mgh.harvard.edu

The relationship between systemic vascular risk, cerebrovascular injury markers, and cognition in older adults at risk of Alzheimer's disease

INVESTIGATORS: W. W. Yau, J. Rabin, R. F. Buckley, M. J. Properzi, J. F. Fu, S. Hsieh, E. Thibault, P. Mojiri-Forooshani, M. Goubran, B. J. MacIntosh, S. E. Black, J. C. Price, K. A. Johnson, R. A. Sperling, J. P. Chhatwal, A. P. Schultz, Z. Shirzadi

Systemic vascular risk is a well-established contributor to late-life cognitive decline, yet the mechanism is not completely understood. We investigated the inter-relationship between neuroimaging-based measures of vascular injury (white matter hyperintensity (WMH) volume, Peak width of Skeletonized Mean Diffusivity (PSMD), and relative cerebral blood flow (rCBF)), systemic vascular risk (Framingham Heart Study cardiovascular disease risk score (FHS-CVD)), and cognitive decline in older adults at risk of Alzheimer's disease using data from the Harvard Aging Brain Study (N=241, age range= 65-89.2, F/M=144/97). We extracted WMH from structural MRI and PSMD from diffusion MRI. We performed kinetic modeling on dynamically-acquired PiB-PET data to extract a proxy of rCBF (PiB-R1). Global cognition was assessed using Preclinical Alzheimer Cognitive Composite (PACC).

We observed a significant correlation between cross-sectional FHS-CVD and cerebrovascular injury markers ($|r|>0.18$, $p<0.01$), yet these variables were not related to the amyloid burden ($p>0.05$). Moreover, the systemic and brain vascular markers were moderately correlated with age as well as gray matter volume ($|r|>0.31$, $p>0.001$). Interestingly, PACC change over time (average follow up time = 7.3 years) was associated with FHS-CVD ($t=-2.2$, $p=0.03$), PiB-R1 ($t=3.4$, $p<0.001$), and PSMD ($t=-3.8$, $p<0.001$) in the people with a lower amyloid burden but not the high amyloid group (adjusted for age, sex, and education). These results demonstrate that vascular injury measures in conjunction with the clinical markers can be used to monitor cognitive decline in older adults at risk of Alzheimer's disease.

Poster Number 137

Shi Sun, PhD
Neurosurgery, Research Fellow | shsun@mgh.harvard.edu

Detailed identification of extracellular neuronal responses in the lateral geniculate nucleus of awake macaques

INVESTIGATORS: S. H. Sun, N. J. Killian, J. S. Pezaris

Have we identified all cell types in the lateral geniculate nucleus (LGN)? Of retinal cells projecting to LGN, only 80% carry signals associated with classic thalamic responses, and we want to identify the missing 20% through rigorous analysis in the LGN of awake monkeys. With the development of multiple-electrode arrays and sophisticated spike-sorting algorithms, we can now simultaneously sample the brain with detailed identification of extracellular signals, which may reveal previously overlooked signals. Using these tools, we attempt to characterize the full range of neuronal responses in the LGN of awake monkeys.

We recorded from 255 single units in the LGN of three macaques using 16-channel electrode arrays and found three distinct classes of extracellular spike waveforms: the commonly reported negative-dominant waveforms (64%); triphasic waveforms (13%) that are also negative but have three phases; and positive-dominant waveforms (23%) that are not often reported in the literature. All units were stimulated with high-resolution visual noise, with 71% having their receptive field (RF) successfully mapped. We correlated the spike classes against their RF and response characteristics to identify any relationships between spike shape and neuronal class (magnocellular, parvocellular, koniocellular or, importantly, other). Out of the remaining LGN cells for which an RF could not be found, 77% responded significantly to the mapping stimulus. Our observations suggest that the population of LGN cells may be broader than traditionally thought. Understanding these often-ignored cells may help identify the previously missing retinothalamic projections.

Poster Number 138

Kathleen Vincent, PhD
Anesthesia, Critical Care and Pain Medicine, Research Fellow | KFVINCENT@mgh.harvard.edu

Chemogenetic activation of dopaminergic midbrain neurons in rats accelerates cognitive recovery following dexmedetomidine- but not ketamine-induced loss of consciousness

INVESTIGATORS: K. F. Vincent, A. Cho, K. Solt

Ongoing work from our lab has established that dopaminergic midbrain neurons, specifically those in the ventral tegmental area (VTA), are involved in restoring consciousness following general anesthesia. Whether these circuits contribute to cognitive recovery following emergence, however, is unknown. Here we targeted expression of excitatory designer receptors exclusively activated by designer drugs (DREADDs) to midbrain dopaminergic neurons in adult Sprague Dawley rats trained in a novel touchscreen-based neurocognitive task, the 5-choice serial reaction time task (5CSRTT). Rats were administered ketamine (50mg/kg, i.v.) or dexmedetomidine (20ug/kg, i.v.) to induce loss of consciousness. Following loss of consciousness, rats were administered either clozapine-N-oxide (CNO, 3 mg/kg, i.p.) to activate DREADDs or saline and placed supine in the cognitive testing chambers. Following the return of consciousness, rats had three hours to perform the cognitive task. Following dexmedetomidine, CNO treatment significantly accelerated cognitive recovery over saline ($\chi2=5.588$, $P=.0104$). Interestingly, CNO has no effect on cognitive recovery following ketamine-induced unconsciousness ($\chi2=0.3793$, $P=.5380$). These data suggest there are distinct mechanisms by which the brain restores cognitive function following anesthetic-induced breaks in consciousness. Identifying these mechanisms will be key to designing effective strategies for facilitating neurocognitive recovery in vulnerable populations.

Poster Number 139

Elnaz Ayatiafin, MD
Obstetrics and Gynecology, Clinical Research Fellow | Elnaz.ayati84@gmail.com

The Effect of Repairing Stage One Apical Prolapse on the Outcomes of the Anterior Vaginal Wall Repair: A Descriptive Study of an Extraperitoneal Uterine Suspension

INVESTIGATORS: E. Ayati, Y. Kim, M. Ortega, S. DeAndrade, K. James, M. Wakamatsu, K. Hung. We sincerely appreciated acknowledged Dr. Marie Bangura and Dr. Joe Shi for their contribution

Objective: To assess the recurrence rate and perioperative outcomes of patients who underwent an extraperitoneal uterine suspension as a non-mesh, uterine-sparing alternative for either stage one apical prolapse or occult apical prolapse not detectable prior to the time of examination under anesthesia.

Methods: A retrospective chart review of patients who underwent an anterior vaginal wall repair with extraperitoneal uterine suspension from 2005 to 2015 was conducted. The primary outcome of interest was a composite of the recurrence data, which was defined as vaginal bulge symptoms, examination showing any compartment pelvic organ prolapse quantification (POP-Q) at 0 or more, or retreatment of POP (pessary, surgery, or referral to physical therapy).

Results: Sixty-one patients underwent an extraperitoneal hysteropexy over 11 years. During the median follow-up period of 83.5 months (IQR 54.4 - 107.2), recurrence of POP was seen in nine women (14.8%). The median time to recurrence was 36.3 months (IQR 14 - 75.5). Recurrence by symptom alone occurred in three women (4.9%), by POP-Q alone in five women (8.2%), and by both symptom and exam in 1 woman (1.6%). Baseline constipation (p=0.04) and preoperative genital hiatus of 5 cm or greater (p=0.01) were significantly associated with recurrence.

Conclusion: About 15% of women who underwent stage one apical repair with concomitant anterior vaginal repair had recurrent prolapse, but none underwent retreatment. Constipation and wide preoperative genital hiatus were associated with a higher recurrence rate.

Poster Number 140

Alexandra Bercow, MD
Obstetrics and Gynecology, Clinical Research Fellow | abercow@partners.org

Utilization of Sentinel Lymph Node Biopsy in Early-Stage Vulvar Cancer: A National Cancer Database Study

INVESTIGATORS: A. S. Bercow, A. Melamed, W. B. Growdon, E. L. Eisenhauer, A. Bregar, G. Molina, C. Minami

Background: Since 2012, sentinel lymph node biopsy (SLNB) has been considered equivalent to standard inguinofemoral lymphadenectomy (IFLD) in select patients with early-stage vulvar cancer. However, uptake of SLNB has been limited and little information exists about factors associated with access to the procedure.

Methods: Between 2012-2018, women with stage IB vulvar SCC were identified using the National Cancer Database. Patient, facility, and disease characteristics were compared between patients who underwent SLNB versus IFLD alone. Multivariable logistic regression analyses evaluated factors associated with SLNB. Kaplan-Meier survival analysis using log rank test and Cox regression were performed.

Results: Of the 3,454 patients, 1,094 (31.6%) did not undergo lymph node evaluation (LNE) and 2,360 (68.3%) underwent LNE with 1,668 (82.0%) undergoing only IFLD and 692 (29.3%) SLNB. On multivariable analysis, patients diagnosed between 2015-2018 were more likely to undergo SLNB than patients diagnosed 2012-2014 (OR 1.86, 95% CI 1.50-2.31). Midwesterners were less likely to undergo SLNB than their Northeastern counterparts (OR 0.70, 95%CI 0.50-0.96). Moderate (OR 1.58, 95%CI 1.18-2.09) and high (OR 2.12, 95%CI 1.56-2.88) volume hospitals were associated with higher rates of SLNB compared to low-volume hospitals. There was no difference in overall survival between patients who underwent SLNB and those who underwent IFLD with negative nodes (HR 0.90, 95% CI 0.70-1.15).

Conclusions: The utilization of SLNB in early-stage vulvar cancer is increasing but utilization varies at the patient, hospital, and regional levels. The lack of survival difference between the two procedures suggests overtreatment in women with negative nodes who underwent IFLD.

Poster Number 141

Nichola Bomani, BA
Obstetrics and Gynecology, Graduate Student | nbomani@mgh.harvard.edu

The Impact of Telemedicine on Minority Women's Access to Gynecologic and Fertility Care during the COVID-19 Pandemic

INVESTIGATORS: N. Bomani, K. James, J. Petrozza

In this study, we seek to understand and quantify how the shift to telehealth affected minority women's access to General Gynecology (GYN) and Reproductive Endocrinology and Infertility (REI) care within the Massachusetts General Brigham (MGB) System. Using data from the MGB Health Equity Dashboard, we analyzed 73,648 completed appointments in GYN and REI from January 2020-August 2021. Appointments were stratified by patient race and modality of appointment. Minority women were defined as women who self-reported as Black, Hispanic/Latina, Multiracial, Asian, or American Indian. Frequency statistics and univariate logistic regression models were used to determine differences in pre- and midpoint-pandemic telehealth volume, minority access, and preferred telehealth modality. A p-value <0.05 was considered statistically significant. Our REI and GYN services experienced a respective 1294% and 1199% increase in telehealth visits during January-March 2021 relative to this same interval in 2020. The shift to telehealth significantly increased minority women's access to GYN services from pre-COVID-19 ambulatory levels (4.8%, p<.0001). We noted a 3% overall increase in the proportion of minority women represented in the REI service (p=0.02) in March 2021 relative to March 2020. Minority women were nearly twice as likely to use Telehealth for REI encounters in this same timeframe (OR 1.72, 95% CI [1.23, 2.42]). Women of Color have historically been underrepresented in REI care despite being overrepresented in the infertility burden. The continued use of telehealth modalities for delivering ambulatory REI and GYN care has the potential to expand REI access to minority women beyond the COVID-19 pandemic.

Poster Number 142

Golnaz Namazi, MD
Obstetrics and Gynecology, Resident | gnamazi@partners.org

Neuraxial analgesia versus liposomal bupivacaine as part of enhanced recovery after surgery: insights from institutional experience

INVESTIGATORS: G. Namazi, K. M. Elias

Background: Pain control is a complex but crucial component of enhanced recovery after surgery (ERAS), yet difficult to achieve. Advances in multimodal analgesia including locoregional anesthesia have improved patient outcome.

Materials and Methods: In this retrospective study, we compared the postoperative outcome and achievement of pain management between intraoperative liposomal bupivacaine (LB) infiltration and thoracic epidural injection in gynecological oncology laparotomy cases from 2017-2020. A total of 657 patients were included, 390 of which received thoracic bupivacaine only epidural injection and 267 patients received intra-operative LB infiltrations.

Results: The overall ERAS compliance was higher in the LB group compared to the epidural group (73.9% vs 66.7%, p-value <0.0001). Patients in the LB group had a overall shorter length of stay (2.4 vs 3.4 days, p-value <0.0001) and required less opioids on post-operative day 2 (p-values <0.0001). Patients in the LB group benefited from earlier mobilization as well as quicker bowel recovery (p-values <0.0001). Post-operative complications during hospital stay including nausea/vomiting and pain were significantly higher in the epidural group (p-value <0.0001).

Conclusion: In conclusion, our data shows that subdermal/subfascial incisional LB injection helped patients ambulate faster with reduced hospital length of stay, narcotic use, or complications.

Keywords: enhanced recovery after surgery; multimodal analgesia; gynecological oncology; laparotomy; epidural anesthesia; liposomal bupivacaine

Poster Number 143

Rachel Cross, BA
Orthopaedics, Clinical Research Coordinator | rcross3@mgh.harvard.edu

Psychosocial and Functional Impact of Digital Replantation

INVESTIGATORS: P. L. DiGiovanni, Y. A. Hoftiezer, B. E. Heijden, K. R. Eberlin, J. Lans, N. C. Chen, Jesse B. Jupiter Research Fund of the Wyss Medical Foundation

Traumatic amputations of one or more digits occur at around 7.5 per 100,000 patient years in the U.S. The main treatment options for these injuries are either surgical amputation or replantation to salvage the digit. Replantation aims to preserve the function of the digit and can have important sociocultural implications as well. This study looked to determine the long-term patient-reported outcomes after successful replantation of at least one digit, as well as determine which factors are associated with differences in such outcomes. This was done by enrolling patients who presented to Massachusetts General Hospital between 2009 and 2019, leading to thirty-six being enrolled. Subjects completed various questionnaires that assessed the physical and mental impacts of their replantations. Patients with significantly worse upper extremity scores tended to have a greater number of injured (p=0.022) or lost (p=0.043) digits, the dominant hand being affected (p=0.007), older age at the time of injury (p=0.049), sustained a traumatic amputation of the ring finger (p=0.025), or required neuropathic pain medication after their replantation (p=0.02080). Additionally, those affected by neuroma rated their changes in household financial situation (p=0.021) and mental wellbeing (p=0.042) as significantly worse compared to patients without neuroma. Regarding long-term symptoms, a vast majority (n=32, 88.9%) reported being affected by cold intolerance in the injured digits, and about half of patients (n=17, 47.2%) still experience some pain in the replanted digits. With this, we show that techniques aimed to reduce neuroma-related pain could be a valuable addition to replantation surgery.

Poster Number 144

Kevin Kooi, MD
Orthopaedics, Clinical Research Fellow| kkooi@mgh.harvard.edu

Factors associated with 30-day soft tissue complications following upper extremity sarcoma surgery

INVESTIGATORS:Y. A. Hoftiezer, J. Lans, B. B. Feniere, K. R. Eberlin, N. C. Chen, S. A. Lozano-Calderón

Background and objectives: The incidence of soft tissue complications following sarcoma surgery in the upper extremity is reportedly high. Therefore, this study assessed the National Surgical Quality Improvement Program (NSQIP) database to identify independent risk factors, while also reporting the incidence of soft tissue complications in the first 30 days after surgery.

Methods: A total of 620 patients that underwent surgical treatment for upper extremity sarcoma were included from the NSQIP database. Soft tissue complications were defined as surgical site infection, wound dehiscence, or soft-tissue related reoperations. Clinically relevant patient and treatment characteristics were selected and analyzed.

Results: The 30-day soft tissue complication rate was 4.7%. In the multivariable analysis, higher body mass index (p = .047) and longer operative times (p = .002) were independently associated with soft tissue complications.

Conclusions: Higher body mass index and longer operative times are risk factors for soft tissue complications following upper extremity sarcoma surgery. The soft-tissue complication rate following resection of upper extremity tumors is low in this national cohort, possibly due to the relatively small tumor size and low prevalence of radiotherapy.

Poster Number 145

Vasundhara Mathur, MBBS
Orthopaedics, Research Fellow | vmathur1@mgh.harvard.edu

The Effect of Race on the Choice of Treatment and its Outcomes in End-stage Ankle Osteoarthritis

INVESTIGATORS: V. Mathur, Y. Sakakibara, J. Kwon, C. DiGiovanni, S. Ashkani Esfahani, D. Guss

Racial equality, an important social determinant of health, has been a concern for policymakers in healthcare. Osteoarthritis (OA) is a common orthopaedic problem that often results in disability, particularly in the elderly. Ankle OA is usually caused by trauma (>70%) and is often found in younger age-groups compared to OA of other sites. Choosing an appropriate treatment, especially in late stages will lower the burden of disability and the associated economic loss. Our rationale is that assessment of healthcare centres is important to determine any possible inequality in health services, with regards to patients' race. The specific aims of this study were to investigate the effect of patients' race on the choice of treatment of end-stage ankle OA, time gap between diagnosis and surgical treatment, duration of hospital stay, post-operative complications and re-operation rates. In our study sample of 509 patients with end-stage ankle OA, 447 (87.82%) patients were whites and 62 (12.18%) were non-whites. Our results showed that the difference in the proportion receiving conservative treatment between whites and non-whites (53.91% vs. 58.06%) was not significant (p=0.54). Race of the patient and time gap between diagnosis and surgical intervention were not correlated (p=0.17). No association was found between race and post-operative complications (p= 0.77) and re-operation (p= 0.85). Lastly, race was not found to be a significant predictor of duration of hospital stay (p=0.32). This study demonstrated that the choice of treatment and post-treatment outcomes for end-stage ankle OA were similar among white and non-white patients in our hospitals.

Poster Number 146

Nour Nassour, MD
Orthopaedics, Research Fellow | nnassour@mgh.harvard.edu

Risk Stratification of Venous Thromboembolism in Patients with Ankle Fracture

INVESTIGATORS: N. Nassour, B. Akhbari , N. Ranganathan, H. Ghaednia , C. W. DiGiovanni, S. Askhani-Esfahani, D. Guss

One of the main causes of mortality among trauma patients in orthopedic settings is venous thromboembolism (VTE). In this study, we used data analysis methods and machine learning to assess the potential risk factors for VTE in patients with ankle fractures. We aimed to develop a predictive model to distinguish high-risk patients for developing VTE after different types of ankle fractures and their treatments.

After screening approximately 16,421 patients with ankle fractures, a total of 882 patients who were suspected of VTE according to their signs and symptoms were recruited, 235 had confirmed VTE (VTE group) and 647 did not have VTE (controls). More than 100 variables such as patient's demographics, medical history notes, fracture characteristics, treatments, medications, and comorbidities, were evaluated using machine learning algorithms. Variables that led to a statistically significant difference between the two groups were included in the final prediction algorithm.

Our results showed that patients with surgical intervention (p=0.002, OR=1.9), open fractures (p=0.001, OR=2.4), smokers (p=0.002, OR=1.4), multiple fractures (p=0.01, OR=1.8), age 18 to 59yo (p<0.001, OR=4.42) and males (p<0.001, OR=1.99) had positive correlation with VTE following ankle fracture when compared to the controls. Longer hospital stays were also correlated with VTE; the average hospital stay was 3.8 days in controls versus 9.7 days in VTE group (p=0.001).

We show that our preliminary prediction model was developed based on factors that had a significant correlation with VTE, particularly hospital stay >3 weeks which was a major distinguishing factor suggesting prophylaxis use in ankle fractures.

Poster Number 147

Amy Berger, BS
Psychiatry, Clinical Research Coordinator | afberger@partners.org

An Evidence-Based Intervention for the Treatment of Comorbid Autism Spectrum Disorder (ASD) and Substance Use Disorder (SUD)

INVESTIGATORS: J. McKowen, J. Towbin, A. Yule, D. Woodward, L. Nowinski, G. Forchelli, R. Meyers, G. Joshi, T. Wilens

BACKGROUND: Recent research has revealed that 3-36% of individuals with autism spectrum disorders (ASD) have substance use disorders (SUD) and 20% of patients who present to SUD programs have traits of ASD. Clinicians who are trained in SUD treatment typically have little training on identifying and treating ASD, and clinicians trained in ASD have little training on identifying and treating SUD. Given that individuals with ASD often have socio-communication issues and significant dependence on family, standard treatment for SUD is not sufficient for this population. However, there are no current interventions for individuals with comorbid ASD and SUD.

METHODS: In order to address the lack of treatment, a multidisciplinary team of psychologists, psychiatrists, and social workers from addiction medicine and behavioral health developed a behavioral therapy intervention for comorbid ASD and SUD through child modules and parent support modules.

RESULTS: We developed 12 child modules, 9 parent modules, and 3 joint modules that integrate evidence-based interventions including ACRA, DBT, CBT, CRAFT, and ASD Social Skills training. This protocol was pilot tested in three youths with comorbid ASD and SUD. After completing the treatment plan, one continued to residential treatment, one remained sober, and one reported cutting down on substance use.

DISCUSSION: This was the first study to develop a treatment approach between ASD and SUD. Overall, preliminary evidence suggests that this is an effective approach to treating comorbid ASD and SUD. Further research is needed to test this protocol in a larger population and compare it to treatment as usual.

Poster Number 148

Cayley Bliss, BA
Cancer Center, Clinical Research Coordinator | ccbliss@mgh.harvard.edu

Exploring resiliency needs and mind-body treatment response among treatment-seeking cancer curvivors and metavivors

INVESTIGATORS: L. F. Fox, C. C. Bliss, A. Rasmussen, E. C. Noonan, D. L. Hall, G. K. Perez, L. Traeger, A. El-Jawahri, A. Comander, J. Peppercorn, R. Anctil, E. R. Park

Although both groups face high stress following initial treatment, little is known about similarities and differences in the needs of cancer "curvivors" (completed curative intent therapy) and "metavivors" (living for years with metastatic disease) for psychological resiliency intervention. Thus, this study explored the relationship between survivorship status (curvivor vs. metavivor) and resiliency at the start of a resiliency intervention as well as with pre-post changes.

Between 2017-2021, 192 survivors (87% female; Mage = 56.1; 89% non-Hispanic White; 83% curvivor) completed online surveys before and after participating in mind-body resiliency groups at MGH. The Current Experiences Scale measured 6 aspects of resiliency: New Perspectives (NP), Personal Strength (PS), Spiritual Connection (SC), Relating to Others (RO), Health Behaviors (HB), and Appreciation for Life (AL). Linear regression models tested cross-sectional (baseline scores as outcome) and longitudinal (post-treatment scores as outcome, controlling for baseline) associations between pre-treatment variables and resiliency.

At baseline, metavivors reported more resilient HBs (D=0.54, p=.001) with no other significant differences in resiliency. In longitudinal analyses (n=96), curvivors gained greater SC (D=-0.37, p=.04) with no other significant differences in resiliency change.

Metavivors and curvivors demonstrated similar baseline resiliency and strength change over time in most domains, suggesting that diverse samples of survivors may benefit from resiliency intervention. Future work may examine differences in participant needs and treatment preferences among diverse metavivors, including variables such as time since diagnosis, time since treatment, and exposure to various survivorship stressors (e.g., transition back to work, fears of recurrence, body image change).

Poster Number 149

Yaen Chen
Psychiatry, Undergraduate Student | ychen133@mgh.harvard.edu

Lower insular cortical thickness and greater parietal surface area among adolescent females with low-weight avoidant/restrictive food intake disorder (ARFID)

INVESTIGATORS: Y. Chen, F. Petterway, C. O. Sailer, H. Carrington, L. M. Holsen, N. Micali, K. Becker, M. Misra, K. T. Eddy, D. L. Franko, E. A. Lawson, J. J. Thomas, A. E. Lyall, L. Breithaupt

The neural circuitry underlying Avoidant/Restrictive Food Intake Disorder (ARFID), a restrictive eating disorder unrelated to body image concerns, is not well understood. Studying the distribution of anatomical abnormalities over the entire cortical surface will aid in understanding ARFID pathophysiology. In this study, we compare cortical thickness (CT) and surface area (SA) between low-weight (low-wt) females with ARFID and healthy controls (HC). We hypothesized differential CT/SA patterns in the orbitofrontal cortex (OFC) and anterior insula, both regions that are associated with reward processing. Using a cross-sectional study design, we processed T1-weighted scans from 49 females (aged 10-21 years, mean = 16.8 ± 3.34 years) diagnosed with low-wt ARFID (n=18) and HC (n=31) with an internal pipeline, which included visual quality control steps, outlier detection, and masking using multi-atlas brain segmentation. Next, we processed masked images using FreeSurfer7, and extracted mean CT and SA for the bilateral insular cortex, occipital, frontal, parietal, and temporal lobes. We assessed between-group differences (low-wt ARFID vs. HC) in bilateral cortical regions using multiple linear regression in R. Estimated total intracranial volume was included as a covariate in all models. Here we found a significant main effect of group on the right insula CT ($F(1, 46)=4.88$, $p=0.032$), such that individuals with low-wt ARFID had lower CT in the insular cortex compared to HC. We also observed a significant difference between groups in the left parietal lobe SA ($F(1, 46) = 4.41$, $p = 0.041$), with greater SA in low-wt ARFID compared to HC.

Poster Number 150

Brett Dolotina, BS
Psychiatry, Clinical Research Coordinator | bdolotina@mgh.harvard.edu

Identity matters: Investigating the relationship between syndemics and sexual risk behavior by MSM subtype in India

INVESTIGATORS: B. Dolotina, J. S. Lee, S. A. Safren, B. Thomas, A. Dange, S. Rawat, M. J. Mimiaga, K. H. Mayer, C. O'Cleirigh

Men who have sex with men (MSM) in India experience high rates of psychosocial difficulties (depression, post-traumatic stress, alcohol use, substance use), which interact synergistically (i.e., syndemics) and result in increased HIV risk. Syndemics and their impact on sexual risk in India have not been explored by MSM-subtype: Kothi (feminine-appearing, predominantly receptive), Double-Decker (both insertive and receptive), and Panthi (masculine-appearing, predominantly insertive). This study sought to (1) characterize syndemics, condomless anal sex acts (CAS), and demographics by MSM-subtype (Kothi, Double-Decker, Gay); (2) examine whether syndemics are associated with CAS; and (3) determine whether the relationship between syndemics and CAS varies by MSM-subtype.

Data come from a randomized clinical trial of 608 MSM at risk of HIV in Chennai and Mumbai, India. ANOVAs were utilized for Aim 1. Multivariate regressions were employed for Aims 2 and 3, adjusting for sex-work and income. Panthis were excluded as part of the study design.

Compared to Double-Deckers and Gay-MSM, Kothis had higher levels of CAS ($F(2,598)=27.36$,$p<0.001$) and sex-work ($F(2,598)=58.39$,$p<0.001$), and lower levels of income ($F(2,598)=6.334$,$p=0.0019$) and employment ($F(2,598)=3.248$,$p=0.0396$). Across the sample, higher levels of syndemics were associated with higher levels of CAS ($\beta=0.27$,$p=0.011$). The interaction of syndemics and MSM-subtype on CAS was also significant ($\beta=-0.359$,$p=0.027$). As levels of syndemics increased, CAS levels increased among Kothis, whereas CAS levels decreased among Double-Deckers.

Poster Number 151

Alexandra Gold, MA
Psychiatry, Clinical Research Fellow | akgold@mgh.harvard.edu

An investigation of impaired risk avoidance among individuals with bipolar disorder

INVESTIGATORS: A. K. Gold, M. W. Otto

Bipolar disorder (BD) is marked by alternating periods of elevated (hypomanic) and depressed mood. Up to 60% of patients with BD experience comorbid substance use disorders (BD+SUD), and BD+SUD is associated with increased morbidity and mortality relative to BD. Given the illness burden in BD+SUD, there is value in evaluating mechanistic processes that underlie these co-occurring conditions, and then targeting these mechanistic processes via treatment. We evaluated one mechanism hypothesized to underlie these comorbid conditions, impairments in risk avoidance, or a tendency to engage in recurring risky behaviors (e.g., HIV risk behaviors, illegal activities) despite negative outcomes associated with such behaviors. Participants with BD (n = 45) or BD+SUD (n = 31) in a relatively non-symptomatic mood state completed various neurocognitive assessments designed to assess risk avoidance and associated cognitive processes. We evaluated differences in BD vs BD+SUD using t-tests and Mann-Whitney U tests as appropriate. We evaluated the relationship between neurocognitive processes and risk behaviors using stepwise forward multiple regression. Here we show that there were no notable between-group differences for BD vs BD+SUD, except for self-reported executive dysfunction which was higher in the BD+SUD group. Collapsing across group, we found that increased discounting of delayed rewards (devaluing a reward with increasing time to reward receipt), an older age, and a younger age of (hypo)mania onset predicted increased clinical risk behaviors (ps < .05). These data suggest the potential value of delay discounting as a modifiable treatment target for BD, both for those with and without comorbid SUDs.

Poster Number 152

Julia Jashinski, MSW
Psychiatry, Clinical Research Coordinator | jjashinski@mgh.harvard.edu

Effects of Cannabis Use Patterns on Insomnia, Pain, and Depression and Anxiety Symptoms: A 9 Month Follow Up

INVESTIGATORS: J. Jashinski, M. E. Cooke, K. Potter, R. M. Schuster, B. Tervo-Clemmens, G. N. Pachas, A. E. Evins, J. M. Gilman

Introduction: Individuals often use cannabis to attempt to alleviate symptoms of pain, insomnia, anxiety, and depression. The extent to which patterns of cannabis use are associated with improved symptoms or development of cannabis use disorder (CUD) is not known.

Method: Data was obtained via 9 monthly assessments in 172 adults who sought to initiate cannabis for pain, insomnia, anxiety, or depression symptoms and participated in a 3-month randomized trial evaluating effects of obtaining a medical cannabis card. We identified five trajectories of cannabis use over nine months post-randomization via an ordinal regression model and a post-hoc classification algorithm, and assessed whether these trajectories were associated with clinical outcomes. Effect sizes (ES) were obtained via model averaging.

Results: Use trajectories were high (H), moderate (M) or low throughout (L), low to high (LH), and high to low (HL). Moderate and high use throughout (weekly or more) were associated with improved anxiety (ES= 0.31[M], 0.33[H]) and insomnia (ES= 0.27[M], 0.32[H]) at nine months. LH was associated with worsened pain (ES=0.28). All trajectories showed increased scores on the CUD identification test (CUDIT-R; ES=0.52-1.24) compared to low use throughout.

Conclusions: In people seeking to use cannabis for medical complaints, we observed a small effect size for reduced anxiety, depression, and insomnia symptoms and for increased pain, and a large effect size for increased CUD severity. These results suggest there are benefits but also risks to using cannabis for symptom relief. Further studies are needed to understand the risk to benefit ratio for cannabis use.

Poster Number 153

Shilei Li
Psychiatry, Undergraduate Student | shli@mgh.harvard.edu

De novo eating disorder diagnoses following a COVID-19 infection: Results from a descriptive retrospective case review using electronic health records from six large hospitals in New England

INVESTIGATORS: S. Friedman-Wellisch, F. Petterway, Y. Chen, K. Eddy, R. Gollub, L. Breithaupt

Current knowledge of SARS-CoV-2 suggests that the infection can have both metabolic and neuropsychiatric effects, suggesting that the infection may impact eating disorder onset and outcomes. We conducted a multi-hospital retrospective descriptive study to characterize de novo eating disorder diagnoses in COVID-19 patients. We identified all SARS-CoV-2 positive admissions across six Eastern Massachusetts hospitals from February 1, 2020 to November 1, 2021 using the Mass General Brigham Research Patient Data Registry and electronic health records. 101,517 individuals tested positive for SARS-CoV-2. Twenty-nine patients (mean age at positive SARS-CoV-2: 39.3 years, range:17.2-66.6 years; 100% female) received a new eating disorder (ED) diagnosis following a positive SARS-CoV-2 test. Of these individuals, 3 had a prior ED diagnosis and experienced diagnostic crossover following SARS-CoV-2 infection (avoidant restrictive food intake disorder (ARFID) to anorexia nervosa (AN); binge-eating disorder (BED) to other specified feeding or eating disorder (OSFED); AN to OSFED). The remaining 26 patients had no prior ED diagnosis before SARS-CoV-2 infection. OSFED was the most frequent diagnosed eating disorder (N=21), followed by BED (N=4), and BN (N=3). The average duration between the positive SARS-CoV-2 test and receiving an ED diagnosis was 4.8 months (sd = 3.14, range: 0.19-12.3). A wide range of SARS-CoV-2 severity was reported, including out-patient management, breathing treatments, and hospitalization. One individual died following COVID-19 and eating disorder complications. In-depth chart review of patients will follow to characterize specific eating disorder symptoms.

Poster Number 154

Maria Lopes, BA
Psychiatry, Clinical Research Coordinator | mlopes6@mgh.harvard.edu

Remotely-Delivered Mindfulness-Based Cognitive Therapy for SCAD Survivors: Study Protocol for an Open Pilot Trial

INVESTIGATORS: M. Lopes, A. Brathwaithe, M. Wood, D. Hall, E. Park, Z. Schuman-Olivier, B. Hoeppner, C. Luberto

Background: Spontaneous coronary artery dissection (SCAD) is an important cause of cardiac events. Approximately half of SCAD survivors struggle with anxiety and fear of recurrence (FOR), contributing to poor sleep and physical inactivity. We adapted Mindfulness-Based Cognitive Therapy (UpBeat-MBCT) for group videoconferencing delivery to target FOR, sleep, and physical activity in SCAD survivors.

Methods: In this open pilot trial, participants will be asked to attend eight weekly 1.5-hour sessions of UpBeat-MBCT delivered via group videoconference, which combines cognitive-behavioral therapy, mindfulness meditation, and cardiac health behavior promotion. Assessments will include surveys of psychological and behavioral variables at baseline and post-intervention; daily diaries of abbreviated survey measures pre-post intervention; and actigraphy monitoring (physical activity and sleep patterns) for 7 days pre-post the intervention. Exit interviews will assess likes, dislikes, and suggestions for improvement.

Results: Recruitment launched in October 2021 and enrollment for the first group was completed in five weeks (n=9). Data collection is ongoing. The primary outcomes are feasibility and acceptability. Feasibility outcomes include feasibility of enrollment, retention, survey completion, actigraphy use, UpBeat-MBCT attendance, and videoconferencing delivery. Acceptability outcomes include ease of completion for surveys and actigraphy, home practice engagement, and program satisfaction. Exploratory outcomes include changes in psychological and behavioral variables and their inter-correlations.

Conclusions: This project is the first and only mindfulness intervention for SCAD survivors and will help inform the development of targeted treatments for this vulnerable group. Results will provide preliminary data for an NIH Stage II efficacy trial to develop an accessible, scalable, and efficacious intervention.

Poster Number 155

Lindsay Nielsen, BS
Psychiatry, Clinical Research Coordinator/Programmer | LNIELSEN@MGH.HARVARD.EDU
Pathways to tobacco cessation in smokers with serious mental illness: a qualitative analysis

INVESTIGATORS: K. M. Schnitzer, A. E. Evins

Most people with serious mental illness (SMI) who smoke tobacco report they want to quit smoking, but few receive safe, effective, evidence-based combinations of pharmacotherapeutic and psychosocial tobacco cessation treatment. Clinical guidance regarding recommended cessation mechanisms (i.e. gradual reduction vs. hard stop) is currently lacking in literature for this population.

We evaluated qualitative data from all 35 participants who were assigned to a community health worker (CHW) and who attained abstinence at the Year 2 endpoint in a large-scale PCORI pragmatic trial (NCT02845440) to gain perspective on successful pathways to tobacco cessation in smokers with SMI.

Detailed CHW visit reports (n=1739) for the 35 smokers with SMI who achieved abstinence were analyzed for: quit mechanisms, cigarettes per day (CPD), cessation aids, and relapse and triggers.

83% of individuals used gradual daily cigarette reduction before making a quit attempt (n=29). At baseline, participants smoked 13 CPD on average and reduced to an average of 4 CPD before successfully quitting. 77% of individuals used a cessation aid, with 70% of those (n=19) utilizing varenicline. 69% of individuals (n=24) relapsed at least once before their final quit. Most common triggers were family stressors, living situations, and barriers to medication access.

Here we show that reducing daily cigarette consumption before attempting to quit may be an effective method for adults with SMI to achieve abstinence. Cessation aids, particularly varenicline, were used by most who achieved abstinence. Clinicians and patients may benefit from knowing that relapse and multiple cessation attempts are common.

Poster Number 156

Julianne Origlio, BS
Psychiatry, Clinical Research Coordinator | joriglio@mgh.harvard.edu
The Role of Mindfulness in a Heated Yoga Intervention for Depression: A Randomized Controlled Trial

INVESTIGATORS: J. Origlio, C. Sorensen, N. Mac Giollabhui, J. Curtiss, B. Hoeppner, C. Streeter, M. Fava, D. Mischoulon, M. Nyer

Introduction: Yoga, exercise, mindfulness, and thermal therapy have each demonstrated antidepressant effects. Bikram Yoga, a type of Heated Yoga (HY), synthesizes these factors through sequenced postures and breathing exercises practiced in 90-minute sessions in a 105˚F room. The current study examines whether mindfulness mediates the effects of a HY intervention on depression.

Methods: 43 adults with depression were randomized to an active HY treatment group (n = 14) or a waitlist control group (n = 29). The active group attended at least two weekly community-delivered HY classes for eight weeks. Depressive symptoms and mindfulness were assessed at baseline, midpoint, and endpoint. Exploratory mediation analysis tested whether treatment group was associated with lower endpoint depressive symptoms via midpoint mindfulness when controlling for baseline depressive symptoms and mindfulness. The indirect pathway was estimated in 5,000 bootstrapped samples using bias-corrected bootstrap confidence intervals.

Results: Participants (M(age) = 32.67 ±11.00) reported moderate baseline depressive symptoms (M = 34.70 ±7.66) and were mostly female, White, non-Hispanic, and college-educated. Treatment group was associated with lower endpoint depressive symptoms via higher midpoint mindfulness (β = 2.73, 95% CI = .049, 5.80). The active group displayed lower endpoint depressive symptoms (β = 1.02, p <.001) and higher midpoint mindfulness (β = -0.78, p <.001).

Conclusions: Findings indicate that increased mindfulness contributed to the ability of the HY intervention to decrease depressive symptoms. Promoting mindfulness may be a key clinical strategy for treating depression. Further exploration of biological and psychological mechanisms in heated versus non-heated yoga is needed.

Poster Number 157

Agata Pietrzak, BA
Psychiatry, Clinical Research Coordinator | apietrzak@mgh.harvard.edu
Social Network Influence on Recovery Pathways among Youth

INVESTIGATORS: A. Z. Pietrzak, S. H. Blyth, P. Krasnoff, E. A. Hennessy

Background: Social influence, i.e., through family, friends, and other social group memberships, is especially important for youth recovering from alcohol and other drug use (AOD). Yet, less is known about how different types of social connections and their characteristics may impact recovery from AOD. To fill this gap in research, we introduced a visual method for capturing social group memberships, Social Identity Mapping (SIM), and assessed its utility as a non-traditional research tool with at-risk youth.

Methods: Twelve adolescents (M=17 years, 83% male) with a history of AOD use completed a SIM and a follow-up interview. SIM data were quantified whereas qualitative data were content analyzed.

Results: Across all members of groups, on average, 32% drank alcohol and 33% used other substances. Larger networks had more conflict (r=0.59), and more casual alcohol use (r=0.81), but less heavy alcohol or substance use (r=-0.72, r=-0.76). Individuals spent less time with groups as the ratio of substance-using to non-using members increased (r=-0.59), and all reported that their recovery-based groups were supportive. While some concluded that group members who used substances were risky to their recovery, others felt that substance-using friends were still supporting their recovery efforts.

Discussion: Support was found for SIM as an engaging measurement tool, highlighting its potential utility with youth populations. The findings also highlighted the importance of assessing several dimensions of social networks in research and clinical settings. Future research in larger, longitudinal samples should investigate how changes in social identity processes impact recovery.

Poster Number 158

Evan Realbuto, BA
Center for Genomic Medicine, Clinical Research Coordinator | erealbuto@mgh.harvard.edu
Exploring the Relationship Between Significant Life Events and Tic Fluctuations in Adults with Tourette Syndrome

INVESTIGATORS: E. R. Realbuto, L. Osiecki , D. Yu, C. M. Mathews, J. M. Scharf

Tourette Syndrome (TS) is a common, childhood-onset neuropsychiatric disorder with significant variability in disease severity and outcomes. However, despite immense patient and family interest in long-term outcomes at the time of diagnosis, there is little data on predictors of future disease severity and persistence of tics and TS-associated co-morbidities into adulthood. The current study proposes to examine data from a recontact study of adults with TS who reported their age of worst tic severity retrospectively. We will first conduct a statistical analysis comparing the adult participants whose worst-ever tic severity occurred in adulthood to those who experienced their lifetime, worst-ever tic severity in childhood or adolescence. Next, among those adults with worst-ever tic severity as adults, we will compare adults who reported the presence of a significant life event (positive or negative) at the time of their worst-ever tics in adulthood with those who did not report a significant life event. Variables to be examined between the two groups will include age, sex, worst ever YGTSS, overall tic impairment score, medication for TS, family history of TS, as well as OCD and ADHD diagnoses. Finally, we will conduct a qualitative analysis examining the categories of life events associated with worst-ever tics. We hypothesize that adults who indicate having a significant life event during the time of worst-ever tics in adulthood will have a significantly higher YGTSS and overall tic impairment score compared to those without a significant life event at the time of their worst-ever tics in adulthood.

Poster Number 159

McKenzie Schuyler, BS
Psychiatry, Clinical Research Coordinator | mschuyler@partners.org

The Educational and Psychosocial Burden of Obsessive-Compulsive Disorder in Youth

INVESTIGATORS: M. Schuyler, S. O'Dor, D. A. Geller

Background: Children with OCD may struggle in school and family environments, with OCD-related impacts on family routines, social connections, and academic performance. To characterize the impact of early-onset OCD on educational and psychosocial domains, we examined functional outcomes in a naturalistic sample of youth with OCD.
Methods: Subjects were 130 children with OCD (Mage = 11.5; 59% male) recruited from an outpatient psychiatry clinic, and 49 non-OCD controls (Mage = 11.7; 53% male) from a contemporaneous study using similar methodology. Youth and parents were administered self-report questionnaires to assess psychosocial functioning (SAICA), relationship quality (FES), and school dysfunction (DICA-R). Linear regression assessed the association between OCD status and FES and SAICA scores, and Fisher's exact test compared proportions of school dysfunction in OCD subjects vs. controls.
Results: FES scores for past familial cohesion were significantly depressed ($p < .05$) in OCD youth compared to controls. Although total SAICA scores were not significantly different between OCD youth and controls, there were significant differences between individual subscales, revealing increased problems with parents ($p < .05$), and less involvement with peers ($p < .01$) and spare time activities ($p < .01$) for OCD youth. Tutoring was needed significantly more often ($p < .01$) in OCD youth than in controls, although rates of repeated grades and special class placement were similar.
Conclusion: Here we offer a portrait of the functional impairment faced by a clinic-based sample of youth with OCD, pointing to significant difficulties in social adjustment and the need for extra support in school.

Poster Number 160

Colleen Sheller, BS
Psychiatry, Research Technician | csheller@mgh.harvard.edu

Optimization of Respiratory-Gated Auricular Vagal Nerve Stimulation for the Modulation of Mood and Anxiety Symptoms in Major Depression

INVESTIGATORS: C. Sheller, R. Staley, H. Aizley, R. Barbieri, V. Napadow, D. Mischoulon, J. M. Goldstein, R. G. Garcia

Recent studies have suggested that a novel neuromodulation technique called respiratory-gated transcutaneous vagus nerve stimulation (RAVANS), which electrically stimulates the auricular branch of the vagus nerve (ABVN), may effectively modulate the stress response circuitry and have beneficial effects on stress response and mood and anxiety regulation in patients with major depressive disorder (MDD). However, optimal stimulation parameters for this technique have not been established. The aim of this study was to identify potential frequency-dependent effects of RAVANS on the regulation of depressed mood and anxiety symptoms in patients with MDD. For preliminary analyses, we report here on the first eleven women (30.0 ± 6.2 yrs) with recurrent MDD and in an active episode included in the study. Subjects underwent five stimulation sessions, during which they received exhalatory-gated stimulation at frequencies of 2, 8, 30, and 100 Hz or sham stimulation, in a randomized order. Subjects completed self-report mood questionnaires including the Beck's Depression Inventory (BDI) and the State-Trait Anxiety Inventory (STAI) at the beginning and end of each stimulation session. RAVANS administration at a 100 Hz frequency was associated with a significant reduction from baseline in BDI scores and STAI scores. The reduction in STAI scores in the 100 Hz session showed a trend toward significance when compared to Sham. No significant effects were identified for other stimulation frequencies. These preliminary results suggest that RAVANS administration at a higher frequency could be more effective on the modulation of mood and anxiety symptoms in MDD patients.

Poster Number 161

Caroline Wisialowski, BA
Psychiatry, Research Technician | cwisialowski@mgh.harvard.edu

Understanding Common PTSD Symptoms in Special Operations Forces Members Endorsing Elevated Alcohol Use

INVESTIGATORS: C. L. Wisialowski, L. H. Brenner, A. V. Morgan, E. J. Lubin, M. A. Iaccarino

Background: Research supports the connection between alcohol misuse and PTSD symptoms in veterans. Special Operations Forces (SOF) represent the most elite in the military due to their intense training and demanding job responsibilities. This population reports a high prevalence of interconnected emotional and physical problems secondary to their work. The current study aims to determine the relationship between PTSD symptoms and self-reported alcohol use among SOF members.

Methods: Participants included 108 treatment seeking SOF service members and veterans attending a 2-week Intensive Clinical Program for PTSD and related conditions. The Alcohol Use Disorders Identification Test - Consumption (Audit-C) and the PTSD Checklist-5 (PCL-5) were used to assess pretreatment alcohol usage and PTSD symptoms. Audit-C question 3 was used to assess binge-like drinking behaviors.

Results: The Audit-C total score (M=3.40, SD=2.58) was compared to different symptom clusters within the PCL-5 (M= 42.21, SD= 18.48). High Audit-C scores correlate most closely with reactivity and arousal symptoms of PTSD (r (106) = .16, p =.089). Patients reporting binge drinking tendencies also reported higher reactivity and arousal symptoms (r (106) = .22, p = .022).

Conclusions: Here we show that while research in conventional military samples supports the association of alcohol use and PTSD symptoms, alcohol misuse nor binge drinking are strongly correlated to PTSD symptoms in SOF members. This population may have diverging mental health presentation and associated risk factors as compared to conventional forces. Larger studies should further explore the relationship of alcohol misuse and PTSD symptoms in this population.

Poster Number 162

Henrique Hadad, MS
Oral and Maxillofacial Surgery, Research Fellow | hhadad@mgh.harvard.edu

Dynamic Self-Regenerating Cartilage (dSRC) from rabbit auricular chondrocytes for temporomandibular joint (TMJ) repair. A proof-of-concept study

INVESTIGATORS: F. Guastaldi, H. R. Matheus, H. Hadad, R. W. Redmond, M. A. Randolph, Fernando Guastaldi was awarded the 2021 HMS Eleanor and Miles Shore Fellowship.

The development of regenerative solutions that focus on the TMJ condyle cartilage has the potential to impact the lives of many. The aim of this study was to evaluate new cartilage matrix using dSRC for TMJ repair. To form the dSRC, freshly harvested rabbit ear chondrocytes were placed into sealed 15-mL polypropylene tubes and cultured on a rocker at 40 cycles per minute for 14 days at 37°C. dSRC samples after 2, 4, and 8 weeks of in vitro culture and samples of native articular cartilage were stained with H&E to evaluate chondrocyte density. Safranin O (glycosaminoglycan: GAG) staining and Toluidine blue (proteoglycan) staining were also performed to assess the biochemical composition of the neomatrix. Consistent formation of dSRC matrix in vitro, in the form of sheets or pellets, after 2, 4, and 8 weeks was observed. H&E staining shows a high cell density in dSRC compared to native cartilage that decreases with increased time in vitro as the matrix matures toward that of native cartilage. All dSRC groups demonstrated intense staining with Safranin O (high GAG production), and intense staining with Toluidine blue (greater proteoglycan content). The viability and successful matrix formation from dSRC were demonstrated in vitro.

Poster Number 163

Henrique Matheus, MS
Oral and Maxillofacial Surgery, Research Fellow | hmatheus@mgh.harvard.edu

Combination of photoactivated gelatin, dental pulp stem cells, and VEGF for skin tissue engineering: in vivo evaluation in the rat

INVESTIGATORS: H. Hadad, F. Zhang, I. A. Rosales, T. Takusagawa, J. Monteiro, F. Guastaldi

Regenerative approaches aiming to enhance the healing capacity of soft tissue barriers may positively impact a variety of fields in medicine. This research aimed to assess a soft tissue engineering approach combining Gelatin-methacryloyl (GelMA), rat dental pulp stem cells (DPSCs), and vascular endothelial growth factor (VEGF) for the regeneration of critical-size skin wounds in rats. Fifteen Sprague-Dawley rats had 4 full-thickness skin defects (10 mm) created on their dorsum. The defects of each animal were randomly assigned to receive one of the following treatments: sham (not filled); GelMa; GelMa+DPSCs; and GelMA+DPSCs+VEGF. Animals (n=5) were euthanized 1, 2, and 4 weeks after treatment. The specimens were collected and headed to conventional histologic processing and paraffin embedding. The sections were stained with hematoxylin and eosin (H&E) and Mason's trichrome. Complete epithelialization of the wounds was observed in few specimens from groups sham and GelMA, opposed to GelMa+DPSCs and GelMA+DPSCs+VEGF, in which most (almost all) wounds were epithelialized by week 2. GelMA+DPSCs+VEGF presented with a higher number of vessels at week 2, which was not observed at week 4. Decreasing cellularity pattern together with increased number and thickness of collagen fibers was observed over time in GelMa+DPSCs and GelMA+DPSCs+VEGF. It can be concluded that loading a carrier with DPSCs combined or not with VEGF improved the healing process of critical-size skin wounds in rats.

Poster Number 164

Briana Burris, DDS
Oral and Maxillofacial Surgery, Clinical Research Fellow | bburris@mgh.harvard.edu

Arthroscopic Management of Synovial Chondromatosis with Skull Base Perforation: A Case Report and Literature Review

INVESTIGATORS: B. J. Burris, F. P. Gustaldi, H. Hadad, W. C. Faquin, J. P. McCain

Purpose: We report the first case of Synovial Chondromatosis (SC) of the temporomandibular joint (TMJ) with skull base perforation treated with minimally invasive surgery. We describe the endoscopic operative maneuvers performed during this TMJ Arthroscopy to diagnose and treat SC.
Case Report: A 34-year-old male presented with 4-years of progressive dental malocclusion and right TMJ pain. Clinical exam was significant for right posterior open bite and deviation of the mandible. Computed tomography demonstrated destruction of the right glenoid fossa without obvious intra-articular lesions. The magnetic resonance imaging revealed numerous hyperintense well-circumscribed lesions, associated with a skull base erosion. Open-surgical management of suspected SC was planned to include a right TMJ diagnostic arthroscopy followed by conversion to open arthroplasty. The endoscopic operative maneuvers detailed in this report, in conjunction with intra-operative Neurosurgery consultation, allowed for accomplishment of the goals of the procedure, completely arthroscopically. Planned conversion to open arthroplasty was deferred during this patient's surgical intervention. Pathology specimens demonstrated classic histologic features of SC: focal nodular arrangements of hyaline cartilage associated with the synovial lining. The patient now reports relief of symptoms and remains on serial observation status post his TMJ arthroscopy.

Conclusion: SC with intracranial extension was historically treated with open arthroplasty of the TMJ. TMJ Arthroscopy is a minimally invasive endoscopic maxillofacial treatment option that, in this case of TMJ SC with skull base erosion, allowed for successful: access to the joint space, harvest of biopsy specimens, retrieval of loose bodies, synovectomy, and patching of skull base perforation.

Poster Number 165

Martin Buta, BA, MD, MS, MBA
Surgery, Clinical Research Fellow | mbuta@mgh.harvard.edu

Efficacy of Mepilex Ag versus Xeroform as a Split-Thickness Skin Graft Donor Site Dressing: Bad Habits Die Hard

INVESTIGATORS: M. R. Buta, J. L. Lisiecki, S. Taylor, M. Tait, N. Farina, J. Levin, J. Schulz, N. Sangji, J. Friedstat, M. R. Hemmila, S. Wang, B. Levi, J. Goverman

Introduction: Split-thickness skin grafting (STSG) is one of the most common procedures in reconstructive and burn surgery. The ideal donor site dressing is one that expedites healing while minimizing pain and infection. Despite numerous studies demonstrating the superiority of moist wound healing, many surgeons continue to treat STSG donor sites dry, with petroleum-based gauze.

Methods: Two burn centers performed a retrospective review of burn patients. Eighty-six patients at Michigan Medicine Burn Center and 270 patients at Massachusetts General Hospital (MGH) underwent STSG with donor sites managed with either a Xeroform® or Mepilex® Ag wound dressing. Infections in both wound dressing groups were documented. In subgroup analysis of Michigan Medicine patients, postoperative pain scores were noted and total opiate usage during hospitalization was calculated. Univariate and multivariate analyses were performed.

Results: In a combined analysis, there was an overall infection rate of 1.2% in the Mepilex® Ag group and 11.4% in the Xeroform® group ($p<0.0001$). On multivariate analysis, patients with Xeroform® donor site dressing had increased odds of donor site infection (OR=10.8, $p=0.002$). In subgroup analysis, there were no significant differences in maximum pain scores between Mepilex® Ag and Xeroform® groups nor were there differences in opiate usage.

Conclusions: STSG donor sites dressed with silver foam dressings have a lower rate of donor site infection relative to those dressed with petroleum-based gauze. Maximum patient-reported pain scores remain similar, as does total opiate usage during hospitalization.

Poster Number 166

Roberto Lorenzi, MD
Surgery, Clinical Research Fellow | rlorenzi-mendez@mgh.harvard.edu

IA Decade of Nipple-Sparing Mastectomy and Immediate Implant-based Breast Reconstruction: Lessons Learned

INVESTIGATOR: R. D. Lorenzi, A. Lin, A. S. Colwell

Background: Nipple-sparing mastectomy is commonly performed for breast cancer treatment or prevention. Prior outcomes research in this field is limited by small sample size and conflicting data.We present one of the largest series in the literature for analysis. Methods: Retrospective single institution review was conducted from 2007-2018. Results:Our query found 2260 implant-based breast reconstructions after nipple-sparing mastectomy including 1508 direct-to-implant and 752 tissue expander-implant reconstructions. The average age was 47 and body mass index 24. The direct-to-implant cohort had more radiotherapy (17.6% vs. 13.2%, $p=0.007$) and chemotherapy (33.1% vs. 25.8%, $p<0.001$) while the tissue expander-implant group had more smokers (9.0% vs. 3.3%, $p<0.001$). Overall complications and nipple necrosis were higher in tissue expander reconstructions compared to direct to implant reconstruction ($p<0.02$ for each).Multivariable regression analysis revealed preoperative radiotherapy (OR 2.99, 95% C.I. 1.827-4.892, $p<0.001$), active smoking (OR 1.86, 95% C.I. 1.132-3.084), and a periareolar incision (OR 3.528, 95% C.I. 1.399-8.893, $p<0.001$) to be the strongest predictors of overall complications and predictors of nipple necrosis ($p<0.05$).Tissue expander reconstruction had a significantly higher odds ratio for complications compared to direct-to-implant (OR 1.488, 95% C.I. 1.106-2.002, $p=0.009$). There was no difference in overall complications between reconstruction with acellular dermal matrix or mesh compared to total or partial muscle coverage without ADM or mesh (OR 0.866, 95% C.I. 0.648-1.157, $p=0.332$). Conclusions:In this large series, radiation, smoking, and incision choice strongly predicted overall complications and nipple necrosis. Direct-to-implant reconstruction and reconstruction with acellular dermal matrix or mesh were not associated with an elevated risk of complications.

Poster Number 167

Monica Majumdar, MD, MPH
Surgery, Research Fellow | mmajumdar1@mgh.havard.edu

Thromboelastography with Platelet Mapping as a Point-of-Care Assay to Identify Infection & Poor Wound Healing Following Lower Extremity Revascularization

INVESTIGATORS: M. Majumdar, S. Lella, R. P. Hall, H. D. Waller, I. McElroy, M. Warner, K. Nuzzolo, B. Sumpio, Z. Feldman, Y. Kim, A. Kirshkaln, A. Dua

Objective. Postoperative infection/dehiscence is higher than expected in peripheral artery disease and contributes significantly to limb loss and mortality. Prothrombotic microvascular pathology has been cited as a contributing factor to poor wound healing. Thromboelastography with platelet mapping (TEG-PM) may provide quantitative insight into one's microvascular coagulation status. This prospective, observational study aimed to determine if TEG-PM could predict poor wound healing/infection following lower extremity revascularization.

Methods. All patients undergoing revascularization between 12/20-1/22 were prospectively included and followed for wound complications or non-surgical-site infections of the index limb. TEG-PM metrics at the first postoperative follow-up in the nonevent group was compared to the TEG-PM sample preceding the diagnosis of infection/dehiscence in the event group. Cox proportional hazards regression and receiver operating characteristic curve analysis was used to model the predictive value of TEG-PM parameters.

Results. Of 102 patients, 18.6% experienced infection/dehiscence. The event group had significantly higher maximum clot amplitude (MA) [47.3mm±16.0 vs. 30.6mm±15.3], higher platelet aggregation [71.3%±27.7 vs. 31.2%±24.0] and lower platelet inhibition [28.7%±27.7 vs. 68.7%±24.1], all $p<0.05$. Regression analysis identified platelet aggregation as an independent predictor of infection [HR=1.04, 95% CI 1.03-1.06]. Cut-points of >33.2mm MA, >46.6% platelet aggregation or <55.8% platelet inhibition identifies those with infection/dehiscence with 79.0-89.5% sensitivity.

Conclusions. These are the first data to provide a quantitative link between prothrombotic coagulation profiles with the development of infection/dehiscence. Based on the cut-points of >33.2mm MA, >46.6% platelet aggregation or <55.8% platelet inhibition, we recommend consideration of an enhanced antimicrobial or antithrombotic approach for these high risk groups.

Poster Number 168

Arian Mansur, BA
Surgery, Graduate Student | amansur@bwh.harvard.edu

The role of adjuvant therapy for localized pulmonary carcinosarcoma

INVESTIGATORS: A. Mansur, L. Shagabayeva, A. Potter, L. Schumacher, C. J. Yang

Objective: Pulmonary carcinosarcoma is a rare and malignant neoplasm of the lung. Data on optimal adjuvant therapy for patients with pulmonary carcinosarcoma are limited. The objective of this study is to determine the potential benefits of adjuvant therapy in patients who undergo complete resection for localized pulmonary carcinosarcoma.

Methods: Overall survival of patients with localized pulmonary carcinosarcoma who underwent complete resection in the National Cancer Database from 2004 to 2017, stratified by adjuvant therapy regimen, was evaluated using Kaplan-Meier and multivariable Cox proportional hazards analysis. Patients treated with induction therapy and those who died within 30 days of surgery were excluded from the analysis.

Results: Of 316 patients who had localized pulmonary carcinosarcoma during the study period, 108 patients (34.2%) underwent complete R0 resection with a 5-year survival of 58.8%. Adjuvant therapy was administered to 22.2% of patients (n = 24), including chemotherapy alone (n = 20), chemoradiation (n =3), radiation alone (n = 1), and no adjuvant therapy (n=84). In unadjusted analysis, compared with surgery alone, adjuvant chemotherapy was associated with significantly improved survival (log-rank P = 0.03). In addition, multivariable Cox modeling demonstrated that treatment with adjuvant chemotherapy (adjusted hazard ratio [aHR] 0.22; 95% CI = (0.08 to 0.63); P < 0.01) was associated with improved survival when compared with no adjuvant therapy.

Conclusions: In this national analysis, surgery followed by adjuvant chemotherapy was found to be associated with a survival benefit when compared to surgery alone in the treatment of pulmonary carcinosarcoma.

Poster Number 169

Floris Raasveld, BS
Orthopaedics, Graduate Student | fraasveld@mgh.harvard.edu

Risk Factors for Neuropathic Pain Following Major Upper Extremity Amputation

INVESTIGATORS: J. Lans, Y. Hoftiezer, S. A. Lozano-Calderón, M. Heng, I. L. Valerio, K. R. Eberlin

Purpose: To identify predictors for development of neuropathic pain following major upper extremity amputation.

Methods: A total of 142 patients who underwent 148 major upper extremity amputations between 2000 and 2019 were retrospectively identified using Current Procedural Terminology (CPT) and International Classification of Diseases(ICD) 9/10 codes. Medical charts were reviewed to collect data regarding explanatory variables. The primary outcome was presence of neuropathic pain. Subcategories included (1) phantom limb pain, (2) phantom limb pain combined with symptomatic neuroma, and (3) symptomatic neuroma.

Results: The mean age was 49.7 ± 15.9 years and 64% were male. The mean follow-up was 4.8 ± 4.2 years. Trauma was the second most common amputation indication, performed in 45 patients (32%). Sixty-two (42%) patients developed neuropathic pain. Thirty-two percent had phantom limb pain, 5.4% had symptomatic neuroma and 4.1% had both. In multivariable analysis, amputations for trauma (odds ratio [OR]: 4.1, p=0.015) compared with oncologic indication, and transhumeral amputations (OR: 3.9, p=0.024) and forequarter amputations (OR: 8.4, p=0.003) compared with amputations at wrist level, were independently associated with neuropathic pain development. No statistically significant association was found between presence of neuropathic pain and demographic variables or comorbidities.

Conclusion: Over 40% of major upper extremity amputee patients develop neuropathic pain. Patients with amputation indication of trauma or an amputation proximal to the elbow have increased risk neuropathic pain development. These patients are most likely to benefit from primary surgical interventions for preventing neuropathic pain, such as targeted muscle reinnervation (TMR) and regenerative peripheral nerve interfaces (RPNI).

Poster Number 170

Roopa Bhat, BS
Medicine, Clinical Research Coordinator | rsbhat@mgh.harvard.edu

Sharing Personal Health Information on Online Self-Diagnosis Platforms

INVESTIGATORS: R. S. Bhat, L. Crawford, N. H. Hong

Introduction: For some people, it can be intimidating or impossible to seek professional medical help if they have disease symptoms. Thus, Internet platforms like Reddit are being used for diagnosis. This study describes the population of people who divulge personal health information on online platforms for self-diagnosis.

Method: We created an online survey that examined the use of and concerns surrounding online self-diagnosis platforms and experiences with posting queries. The survey was posted on various Subreddits (topic-specific communities on Reddit). Responses were collected over 3 months. Participants who completed the survey and consented to being contacted were interviewed. The posters (who have made personal posts) were asked about the platform used, content of the post, and motivations for posting. The observers (who have passively interacted with these platforms) were primarily asked about their reasons for not posting.

Result: Of the 25 respondents 100% have used websites to search for symptoms, but only 33% made a personal post on an online platform. Observers were primarily concerned about data privacy while posters were concerned about anonymity. The main attraction of seeking medical advice online was the fast response rate and convenience. The top reason for not posting was that answers from general searches were sufficient. Anonymity, distrust of physicians, and prior experience with platforms play a role in sharing personal health information online for self-diagnosis.

Conclusion: Tech-savvy adults are more likely to post on online platforms about sensitive or highly specific topics for convenience, fast response, and a sense of community.

Poster Number 171

Edwina Abou Haidar, MBBS, MS
Neurology, Research Fellow | eabouhaidar@mgh.harvard.edu

Therapeutic efficacy of gene therapy for tuberous sclerosis type 2 by delivery of AAV encoding a condensed form of tuberin (cTuberin) in a mouse model

INVESTIGATORS: E. Abou Haidar, S. Prabhakar, P. Cheah, A. Stemmer-Rashmikov, C. Maguire, V. Ramesh, X. Breakefield

Tuberous sclerosis complex (TSC) is an autosomal dominant disorder caused by a hereditary loss of function mutation in one of two tumor suppressor genes, TSC1 and TSC2, encoding for hamartin or tuberin respectively. In TSC-related lesions, the loss of either proteins causes over activation of mTOR signaling, subsequently leading to cellular proliferation and overgrowth in many vital organs, most commonly affecting the brain, kidneys, skin, heart and lung. Neurological features of the disease include seizures, cognitive impairment and autism. Gene therapy using an adeno-associated virus (AAV) vector carrying a "condensed" form of human tuberin (cTuberin) appears to be a promising therapeutic strategy for TSC2. A mouse model of TSC2 generated by AAV1-Cre recombinase disruption of homozygous Tsc2-floxed alleles at birth (P0) has a shortened lifespan (mean 50 days) and brain pathology consistent with TSC, including overgrowth of ependymal/subependymal tissue and enlarged ventricles. Here we show that when these mice were then single injected intravenously at post-natal day 21 (P21) with an AAV9 vector encoding cTuberin, most survived for more than 120 days (ongoing) compared to Everolimus, an mTOR inhibitor used clinically to treat TSC patients, which only extended lifespan when continuously administered. Further immunostaining assays show that AAV9 vector transduced cells throughout the brain and post treatment pathologic assessment of the brain shows normal features. These studies demonstrate the potential of treating life-threatening TSC2 lesions with a single intravenous injection of AAV9-cTuberin as compared to the alternative drug treatment currently in use clinically.

Poster Number 172

Grace Addy, BS
Neurology, Clinical Research Coordinator | gaddy@mgh.harvard.edu

RNS60 in ALS: Expanded Access Program

INVESTIGATORS: D. Gelevski, M. L. Rohrer, J. L. Scalia, M. J. Yerton, M. Doyle, N. Parikh, A. Ellrodt, K. Burke, E. Sinani, H. Yu, A. Sherman, J. Mock, A. Kalmes, K. Hanus, C. Baecher-Allan, M. Adler, B. Wainger, K. Nicholson, J. Berry, S. D. Luppino, S. Paganoni, M. E. Cudkowicz, Healey Center for ALS at Massachusetts General Hospital and Revalesio Corporation

Background: RNS60 is an electrokinetically altered aqueous fluid composed of saline and oxygen that has demonstrated neuroprotective and anti-inflammatory effects in both in vitro and in vivo models of ALS. We designed an Expanded Access Program (EAP) to treat up to 70 PALS who do not qualify for clinical trials with RNS60. The objectives of this ongoing EAP are to provide investigational treatment of RNS60 to PALS, establish the feasibility of EAPs in PALS, and to monitor the safety and tolerability of long-term RNS60 administration.

Methods: Participants receive twice daily inhalation of nebulized RNS60 for up to three years. Safety is monitored through the collection of safety labs and the assessment of adverse events. We administered the ALS functional rating scale revised (ALSFRS-R), measured slow vital capacity, and collected patient-reported experience questionnaires. Blood samples are collected for the measurement of soluble biomarkers in plasma and for functional assessment of regulatory T cells.

Results: 66 PALS have been enrolled and treated with RNS60 for up to 34 months. Average age at baseline was 60.8 and average ALSFRS-R at baseline was 19.7. 18 participants have died due to ALS disease progression. No serious adverse events related to RNS60 have occurred.

Conclusions: This EAP demonstrates the feasibility of performing EAPs in PALS as a complimentary approach to controlled clinical trials that allows for the collection of longer-term safety data. Overall, tolerability for and compliance with RNS60 treatment were high, which demonstrates the feasibility of RNS60 treatment in a broad ALS population.

Poster Number 173

Jennifer Camacho, BA
Medicine, Enrichment Program Manager | jncamacho@mgh.harvard.edu
Highlighting Animal Models of Biomedical Research

INVESTIGATORS: J. Camcaho, M. Hogan, A. Mikkola, A. Slate, Center for Comparative Medicine

Biomedical research using animal models is a vital part of scientific discovery and medicine. Research with animal models is used to improve clinical care, treat disease and disorders, ease pain and suffering, and extend lifespans. The notion of using animals for biomedical research is regarded poorly by the public, often due to misinformation portrayed by extremist groups and media's exaggerations of living conditions and care. In actuality, research animals are provided with a high quality of care and complex living environments complete with comforts to maintain health and wellness. Some very notable accomplishments using animal models have been conducted right here at the Massachusetts General Hospital! MGH has contributed to the body of science that has allowed for successful xenotransplantation of swine organs into humans, helping to provide treatment to the more than 107,000 people that wait on the organ transplantation list each year. MGH provides translational cancer care, involving the implantation of aggressively growing cancer tumors in mouse models to produce a successful treatment regimen in just a few short weeks. Along with the world, MGH contributed to Covid-19 research, resulting in the rapid development of treatments and vaccines which continue to evolve with each new variant. Without animals in research these accomplishments would not be possible. For this poster, we want to highlight the vital role that animals play in research, the high quality of care given by caretakers, and the tireless efforts of post-doctoral, graduate research staff.

Poster Number 174

Dario Gelevski, BS
Neurology, Clinical Research Coordinator | dgelevski@mgh.harvard.edu
IC14 in ALS: Expanded Access Program

INVESTIGATORS: D. Gelevski, G. C. Addy, M. L. Rohrer, C. M. Cohen, J. R. Carey, J. L. Scalia, M. J. Yerton, M. Doyle, N. Parikh, A. S. Ellrodt, K. M. Burke, E. Sinani, Y. Hong, A. Sherman, J. M. Agosti, G. L. Redlich, P. Charmley, D. Crowe, M. W. Appleby, B. Zieglaar, K. Hanus, C. Baecher-Allan, O. Venezia, J. Moon, K. Nicholson, S. Paganoni, J. D. Berry, S. L. Luppino, M. E. Cudkowicz, Healey Center for ALS and Implicit Biosciences, Ltd for providing study drug (IC14)

Background: IC14 is a chimeric anti-CD14 mAb that decreases neuroinflammation by improving T-regulatory cell function. We designed an expanded access program to provide participants with ALS access to IC14 and to learn more about the safety in patients dosed chronically.

Methods: Participants received intravenous infusions of IC14 every two weeks at MGH or locally.. We collected safety labs, amyotrophic lateral sclerosis function rating scale revised (ALSFRS-R), slow vital capacity (SVC), and performed physical, neurologic, and ophthalmologic exams. Blood was collected to determine monocyte mCD14 receptor occupancy (%RO), soluble CD14, anti-drug antibodies (ADA), and T-reg activity.

Results: Average age, ALSFRS-R, and SVC score at screening was 59 (±8.5) years, 29.5 (±9.8) and 62.7% (±28.9), respectively. Participants received IC14 up to 87 weeks. No SAEs were deemed related to study medication. Four participants died due to ALS disease progression. Monocyte mCD14 %RO increased for all participants after IC14 infusions. T-reg suppression activity almost doubled from baseline in multiple participants measured. No sustained ADA levels were detected by 41 weeks.

Conclusion: Chronic IC14 infusions were safe and well tolerated when administered for up to 87 weeks. IC14 was successfully administered at home during COVID-19. TEAEs were uncommon, mild, and self-limited. Measuring RO in real time for each patient guided the adjustment of dosing frequency. Preliminary data suggest an effect on T-reg function. Data collected in this EAP helped inform dosing frequency, however, additional studies are ongoing to determine an optimal IC14 dose to achieve desired levels of RO (e.g. >90%).

Poster Number 175

Martina Nebbia, MD
Surgery, Research Fellow | MNEBBIA@mgh.harvard.edu

B7-H3 targeted CAR-T cell immunotherapy for primary and multi-focal/metastatic intrahepatic cholangiocarcinoma

INVESTIGATORS: S. Shahrzad, G. Lionetto, M. Ventin, C. R. Ferrone, S. Ferrone

The lack of effective therapy for ICC has prompted us to develop a novel immunotherapy using T-cells engineered with a chimeric antigen receptor (CAR-T cells). The aim of this study is to show that B7-H3.CAR-Ts are safe and effectively eradicate primary and multi-focal/metastatic ICC established in NSG mice and prolong their survival.
Primary ICC was established in 20 NSG mice by orthotopically grafting human ICC cells ICC3-GFP-Luc. Then mice were randomized into treatment group (tail vein injection of B7-H3.CAR-Ts), control group (CD19.CAR-Ts) and untreated. The multi-focal/metastatic model was generated by infusing ICC3-GFP-Luc via tail vein; mice were randomized into 2 groups (B7-H3.CAR-Ts/untreated). Tumor size and development of metastasis were monitored by bioluminescent imaging.
B7-H3.CAR-Ts administered via tail vein injection (i.v.) effectively controlled tumor growth in all the treated mice and significantly prolonged their survival ($p < 0.0001$). Specifically, B7-H3.CAR-Ts (5x106/mouse) completely eradicated ICC3 tumors in 88% of the treated mice, which remained tumor free for at least 60 days without any evident side effects.
The antitumor activity of B7-H3.CAR-Ts was also tested in a multi-focal/metastatic ICC model generated by infusing ICC3-GFP-Luc cells i.v. into 8 NSG mice. B7-H3.CAR-Ts completely eradicated ICC3 tumors in all the treated mice which became tumor free already 7 days post-treatment

Here we show that B7-H3.CAR-Ts are effective in eradicating both primary and multi-focal/metastatic disease established in NSG mice and in prolonging their survival, without causing side effects. These results represent a useful background for the translation of the developed strategy to a clinical setting.

Poster Number 176

Hoang Kieu Chi Ngo, PhD
Neurology, Research Fellow | hkngo@mgh.harvard.edu

Short-term Lipopolysaccharide Treatment Leads to Astrocyte Activation in LRRK2 G2019S Knock-in Mice without Loss of Dopaminergic Neurons

INVESTIGATORS: H. Le, S. J. Ayer, G. F. Crotty, M. A. Schwarzschild, R. Bakshi

The G2019S mutation in LRRK2, which enhances kinase activity of the protein, confers a substantial risk of developing Parkinson's disease (PD). However, the LRRK2 G2019S mutation demonstrates an incomplete penetrance, suggesting the involvement of other genetic or environmental factors. Here, we investigate whether the LRRK2 G2019S knock-in (KI) mice exhibit increased nigral neuronal loss trigged by exposure to the inflammogen lipopolysaccharide (LPS), a paradigm that reportedly led to the loss of dopaminergic neurons in mice. We showed that the short-term (2 weeks) treatment with LPS did not cause the nigrostriatal dopaminergic neuronal loss of both wild-type (WT) and the LRRK2 G2019S KI mice. However, the mutant LRRK2 G2019S KI mice showed an increase in phosphorylation of LRRK2 at the autophosphorylation site Serine 1292, which is known as a direct readout of LRRK2 kinase activity when challenged with LPS. Furthermore, treatment of the LRRK2 G2019S KI mice with LPS caused delayed weight recovery and increased levels of glial fibrillary acidic protein (GFAP), a marker of activated astrocytes, which are increasingly recognized as an important player in PD pathogenesis, when compared to wild-type (WT) controls. Administration of caffeine, which is associated with resistance to PD among LRRK2 mutation carriers, attenuated the astrocyte activation in the LRRK2 G2019S KI mice but not WT counterparts. In summary, our findings suggest that the short-term exposure to LPS does not suffice to cause a dopaminergic neuronal loss in LRRK2 G2019S KI mice but result in an increase in astrocyte activation, which could be ameliorated by caffeine.

Poster Number 177

Emad Salman Shaikh, MD
Medicine, Clinical Research Fellow | esshaikh@mgh.harvard.edu

Effect of Combined Tobacco Use and Diabetes Diagnosis on Prevalent Fibrosis among NAFLD Patients

INVESTIGATORS: O. Balogun, J. Y. Wang, E. Shaikh, S. Stoyanova, Z. N. Memel, T. G. Simon, K. E. Corey

Several studies have independently investigated measures of effect and association between cigarette smoking, diabetes, and NAFLD. However, the effects of the interaction between tobacco consumption and diabetes diagnosis on prevalent NAFLD severity remains underexplored. In this study, we aimed to understand the association between the combined risk factor and hepatic fibrosis risk in non-smokers with diabetes. A single-center retrospective cross-sectional analysis of patients from the Mass General Brigham transient elastography (FibroScan) database was performed. Hepatic steatosis and fibrosis stages were assigned using controlled attenuation parameter and liver stiffness measurement scores. Bivariable and multivariable models were developed to explore the associations between three different exposure groups (diabetes and tobacco use, diabetes and no-tobacco use, and no-diabetes and no-tobacco use) and hepatic fibrosis risk (as assessed by FIB-4 index and APRI score). Our analysis revealed a significant independent association between DM and combined smoking and diabetes diagnoses, age, gender, metabolic syndrome, aspirin use, statin use, AST, A1C, total bilirubin exposures and the outcome of interest, fibrosis risk. In the adjusted FIB-4 multivariable model, cigarette smoking, and diabetes interaction had higher odds of fibrosis (aOR, 3.04; 95% CI, 1.62 – 5.76) compared to participants with diabetes only (aOR, 2.28; 95% CI, 1.37 – 3.85). Although DM was independently associated with hepatic fibrosis among NAFLD patients, the interaction between tobacco consumption and diabetes diagnosis revealed a higher likelihood of developing fibrosis. Therefore, lifestyle change via smoking cessation in people with diabetes would be beneficial in reducing liver fibrosis incidence among individuals with NAFLD.

Poster Number 178

Kazuhide Shimizu, PhD
Neurosurgery, Research Fellow | kshimizu3@mgh.harvard.edu

Photodynamic oncolytic virotherapy incorporating genetically encoded photosensitizer KillerRed for the treatment of central nervous system malignanciesa

INVESTIGATORS: K. Shimizu, H. Wakimoto

Background: Photodynamic therapy (PDT) is a targeted cancer therapy utilizing tumor-specific photosensitizers that generate reactive oxygen species (ROS) upon receiving specific light. Our study aims to combine a genetically engineered oncolytic herpes simplex virus (oHSV) armed with a photosensitizer (KillerRed) to establish photodynamic oncolytic virotherapy (PDT-oHSV) that enhances tumoricidal efficacy as a novel treatment approach to deadly CNS neoplasms.

Methods: oHSV expressing KillerRed (G47Δ-KR) was constructed by a bacterial artificial chromosome-based method. In vitro efficacy of KillerRed-mediated PDT was tested by cell viability and cell death assays using human glioblastoma and malignant meningioma cell lines. ROS generation triggered by PDT-oHSV was evaluated by cellular ROS assay. Viral infection and replication in vivo were examined by histological analysis of xenograft mouse models generated with glioblastoma and meningioma cells. The therapeutic efficacy of PDT-oHSV using laser irradiation was assessed in the same xenograft models.

Results: KillerRed-transduced cells emitted red fluorescence in response to 580-590nm amber color LED irradiation. In vitro, amber LED light irradiation after infection with G47Δ-KillerRed induced increased inhibition of cell viability, cell death associated with cell membrane disintegrity, and ROS production compared with G47Δ-KillerRed without light or light alone. In vivo, G47Δ-KillerRed spread well within the tumors, and PDT-oHSV suppressed tumor growth and induced durable remission in some animals bearing human glioblastoma and meningioma xenografts.

Conclusions: We demonstrate that G47Δ-KillerRed-mediated PDT-oHSV is an effective treatment modality that warrants further development.

Poster Number 179

Katherine Stalnaker, MS
Wellman Center for Photomedicine, Research Technician | kstalnaker@mgh.harvard.edu

In vivo wound modeling in pigs: a new method for studying wounds in plantar skin

INVESTIGATORS: K. J. Stalnaker, C. Fuchs, A. Slate, J. N. Camacho, L. Pham, Y. Wang, R. R. Anderson, J. Tam, MGH Center for Comparative Medicine and Knight Surgical Center

Diabetic foot ulceration (DFU) is one of the greatest chronic burdens on the United States healthcare system, annually affecting millions of patients and accounting for billions of dollars in medical expenses. DFUs are also the leading cause for nontraumatic lower limb amputations, which are associated with 5-year mortality rates of about 50% - far surpassing many types of cancer. Previous studies in DFUs have focused on how diabetes affects wound healing, while (to the best of our knowledge) there have not been investigations into whether wound healing differs in plantar skin from hair bearing skin, despite long-standing recognition that plantar skin harbors many specializations, including a greatly enhanced baseline turnover rate, unique compositional and structural adaptations for load bearing, and complete lack of hair. The aim of our study was to develop an in vivo wound model to study plantar wound healing. One of the main challenges was the difficulty in maintaining wound dressings, as animals generally have a low tolerance for wearing bandages on their feet. With assistance from the MGH Center for Comparative Medicine, we developed a positive reinforcement-based behavioral training regimen that successfully induced tolerance towards plantar dressings in swine, which in turn enabled, for the first time, in vivo study of the wound healing process in this highly unusual skin type.

Poster Number 180

Jeffrey Wang, BS
Medicine, Clinical Research Fellow | jywang@mgh.harvard.edu

Menopausal status is independently associated with hepatic fibrosis risk in individuals with non-alcoholic fatty livery disease.

INVESTIGATORS: J. Y. Wang, O. Balogun, Z. N. Memel, E. S. Shaikh, S. Stoyanova, W. Park, T. G. Simon, K. E. Corey

A higher prevalence of non-alcoholic fatty liver disease (NAFLD) has been demonstrated in post-menopausal women compared to pre-menopausal women. The increased occurrence among this subpopulation has been linked to decreased estrogen levels, reduced sex hormone-binding protein, and a relative increase in androgen levels (above the normal reference range). The objective of this study was to explore the associations between estrogen exposure and the prevalent severity of NAFLD. A single-center cross-sectional study of eligible women diagnosed with NAFLD was conducted. Three hundred and twenty-nine female (329) participants aged 18 to 75 years who underwent examination by a FibroScan were enrolled. Descriptive and inferential statistics were performed to compare the difference in vibration-controlled transient elastography-derived liver stiffness and FIB-4 scores among the exposure group. We further used the FIB-4 index to classify the probability of fibrosis as 'low risk' (FIB-4 <1.45) and 'high risk' (FIB-4 >=1.45). At the evaluation, 90 participants had prevalent hepatic fibrosis risk. During our analysis, the Liver Stiffness Model multivariable model (adjusting for age, BMI, tobacco use, hypertension, diabetes, dyslipidemia, and medications) showed postmenopausal women were two times more likely to have prevalent fibrosis (aOR 2.26, 95% CI: 0.59 – 9.36). The FIB-4 multivariable model revealed post-menopausal women were significantly associated with fibrosis (aOR 4.86, 95% CI: 1.56 – 21.4) compared to pre-menopausal participants. Hypertension and BMI were also significantly associated with the probability of prevalent fibrosis. In summary, our findings show that estrogen is associated with a lower prevalence of hepatic fibrosis among individuals with NAFLD.

Poster Number 181

Yongtao Wang, PhD
Surgery, Research Fellow | Yongtao.Wang@MGH.HARVARD.EDU

Inhibiting methionine aminopeptidase 2 prevents liver fibrosis and hepatocellular carcinoma

INVESTIGATORS:Y. Wang, M. Sojoodi, G. Qiao, S. C. Barrett, L. Zukerberg, K. Kuruppu, I. R. Eissa, M. Qadan, M. Lanuti, K. K. Tanabe

Background: The methionine aminopeptidase 2 (MetAP2) pathway, a key regulator of angiogenesis, has been implicated in non-alcoholic steatohepatitis and cancer. MetAP2 inhibition suppresses cancer cell proliferation and xenograft tumor growth. In this study we investigated the hypothesis that MetAP2 inhibition can prevent liver fibrosis and hepatocellular carcinoma (HCC) by inhibiting angiogenesis and neo-vascularization.

Methods: Male Wistar rats received weekly intraperitoneal injections of 50 mg/kg diethylnitrosamine (DEN) for 18 weeks. Rats were randomly assigned to 4 groups after 8 weeks: 1) water (control); or 2) ZGN1345 by daily gavage; 3) 0.15% DMSO (control); or 4) ZGN1136 by daily subcutaneous injection. Fibrosis, tumor nodules and angiogenesis were investigated with molecular and histologic assessments. RNA Sequencing was performed to detect the global transcriptomic landscape in rat HCC. Human HSCs and ex vivo Precision-Cut Liver Slices (PCLS) from human cirrhotic liver were assessed after MetAP2 inhibition.

Results: MetAP2 expression increased in cirrhotic liver and HCC compared with corresponding controls, in both clinical HCC patients with cirrhosis and DEN rat models. MetAP2 inhibition improved ALT, AST and liver fibrosis. MetAP2 inhibition reduced tumor nodule number, PCNA expression, angiogenesis and neo-vascularization. Inhibiting MetAP2 reversed the global transcriptomic landscape of DEN-induced HCC and pathological angiogenesis. MetAP2 inhibition not only inhibited TGF-β1-induced pro-fibrogenic genes in human HSCs, but also inhibited fibrosis in human cirrhosis PCLS.

Conclusions: MetAP2 inhibition effectively prevented cirrhosis and HCC, which was linked to inhibited angiogenesis and neo-vascularization. These data suggest that inhibition of MetAP2 may represent a new prevention target for cirrhosis and HCC.

Poster Number 182

Allison Winter, BS
Neurology, Clinical Research Coordinator | gckane@mgh.harvard.edu

Overview of the Healey Center's Expanded Access Protocol Programs for Investigational Treatments in Amyotrophic Lateral Sclerosis

INVESTIGATORS: M. Yerton, M. Rohrer, J. R. Carey, D. Gelevski, G. Addy, G. Kane, M. Doyle, N. Parikh, A. Ellrodt, K. Burke, A. Sherman, E. Sinani, D. D'Agostino, H. Yu, J. Scalia, D. Sawicki, S. Luppino, S. Babu, S. Chew, K. Nicholson, S. Paganoni, J. D. Berry, M. E. Cudkowicz, Healey Center for ALS at Massachusetts General Hospital, Boston, MA, USA

Background: Expanded access protocols (EAPs) bridge the gap between formal clinical research and clinical care. Advanced ALS patients are often excluded from clinical trials, which focus on evaluating impact on early disease trajectory. EAPs offer patients ineligible for clinical trials access to experimental treatments while also providing useful safety and treatment-related biomarker data that can be utilized for drug development.

Objectives: Provide investigational treatments to advanced ALS patients who do not qualify for clinical trials.
Methods: Successful EAP programs require study staff to safely provide treatment under FDA and IRB oversight. The Healey Center for ALS at Massachusetts General Hospital manages 9 EAPs, including 3 single-patient and 6 intermediate protocols. For larger EAPs, investigators utilize standardized patient-centric electronic data capture (EDC) platform, NeuroREACHTM.

Results: Between July 2018 and May 2021, 130 ALS patients enrolled in the Healey Center's EAPs, with 93 male and 37 female participants. Average time from symptom onset to screening was 59 months. 91 patients had limb-onset ALS, 30 had bulbar, and 6 patients had "other". During the coronavirus pandemic (COVID-19), we updated the programs to initiate remote consenting. Study staff complete visits via telephone and participants conduct other outcomes at a local laboratory.

Conclusions: Although COVID-19 introduced numerous challenges, our adaptive response allowed continuous participant access to medications and safety monitoring in a manner that protected patients and staff from risk. Our innovations in virtual visit follow-up and approaches to ease participant burden may prove to be helpful for trials in ALS and other neurological disorders.

ECOR Administrative Offices | 125 Nashua Street, Suite 822 | Boston, MA 02114 | ecor@mgh.harvard.edu