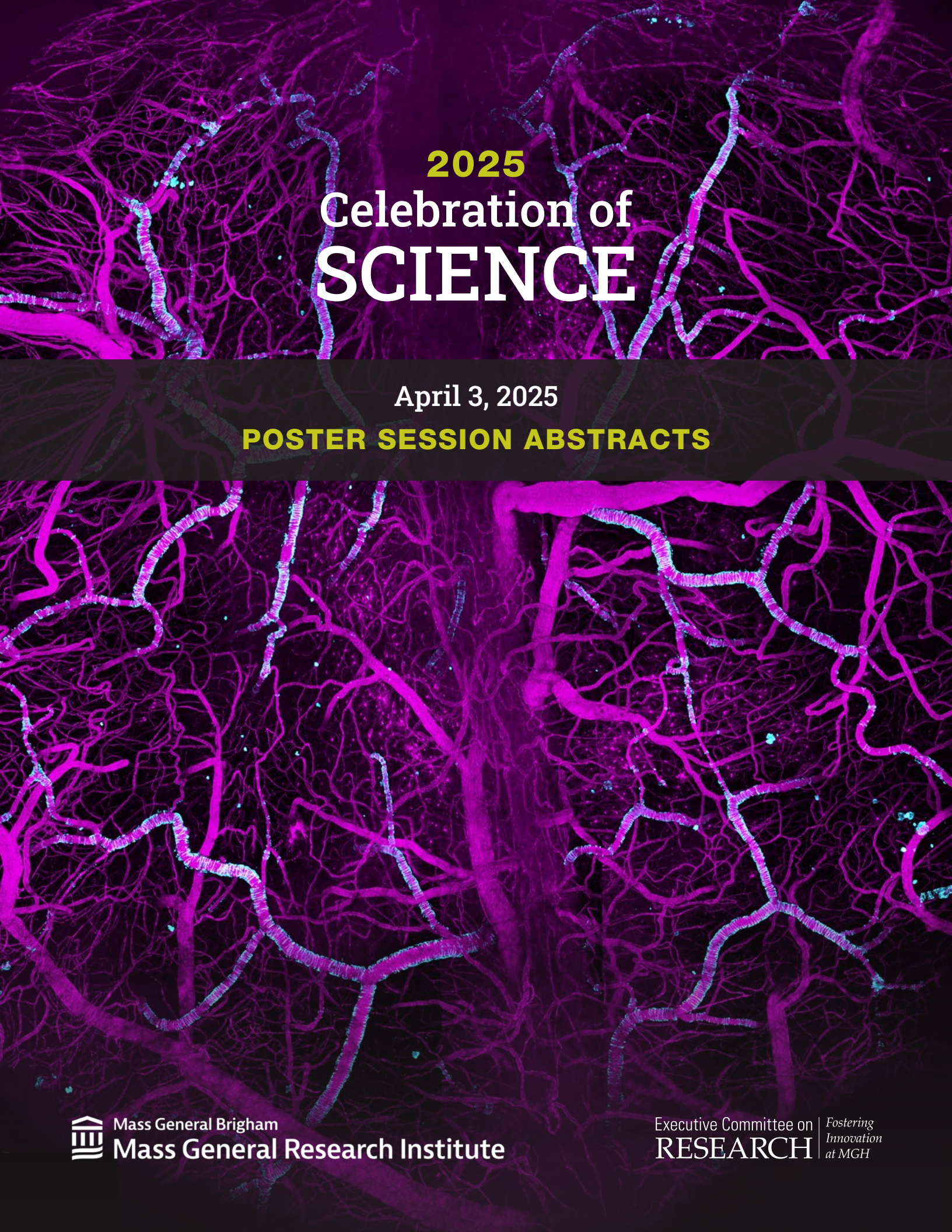


2025 Celebration of SCIENCE

April 3, 2025

POSTER SESSION ABSTRACTS

Mass General Brigham
Mass General Research Institute

Executive Committee on RESEARCH | *Fostering Innovation at MGH*

Agenda

Thursday, April 3, 2025

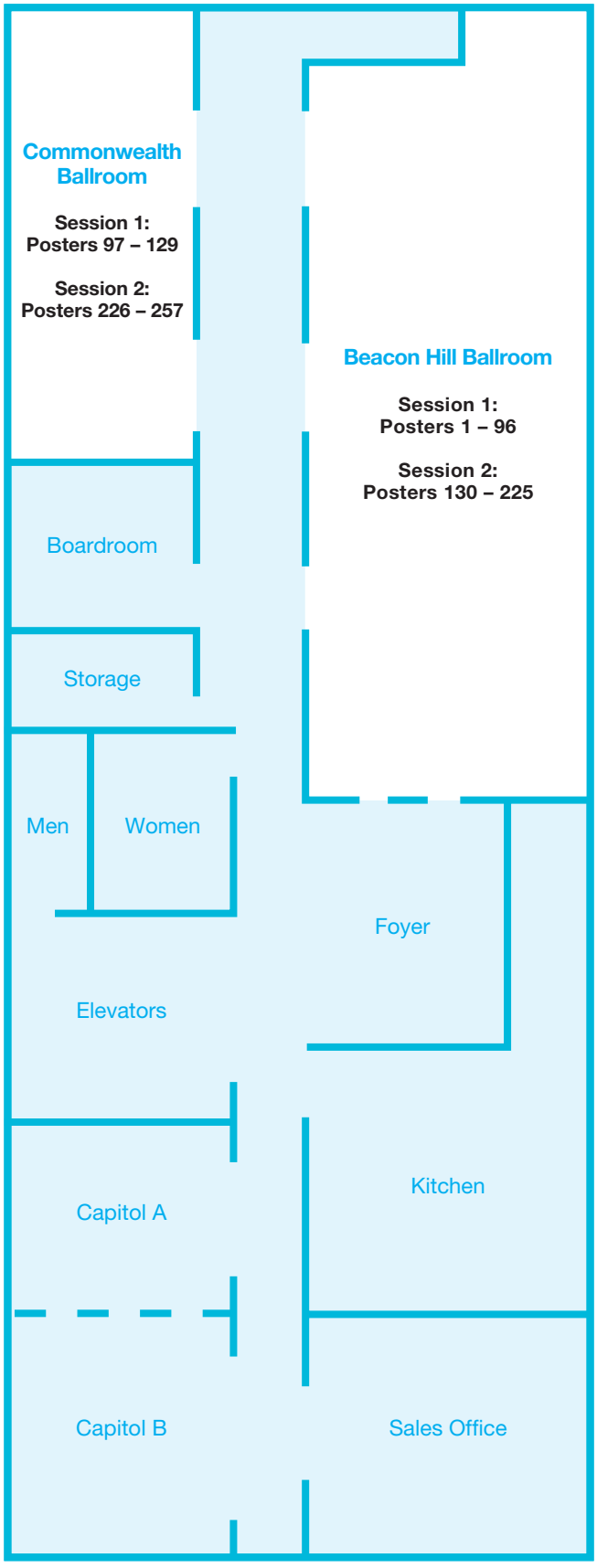
10:00 AM – 1:00 PM	**Poster Session**
2:00 PM – 5:00 PM	**Celebration of Science**
2:00 PM – 2:05 PM	**Welcome and Introduction** Robert Kingston, PhD, Chief Academic Officer, Massachusetts General Hospital
2:05 PM – 2:20 PM	**Celebrating the Science at MGH in 2024** Maurizio Fava, MD, Chair, Executive Committee on Research (ECOR)
2:20 PM – 2:45 PM	**Howard M. Goodman Fellowship** **Epigenetic Reprogramming of CD8 T cell Dysfunction in Cancer** Debattama Sen, PhD, Assistant Professor, Medicine, Krantz Center for Cancer Research, Massachusetts General Hospital
2:45 PM – 3:10 PM	**Martin Prize for Clinical Research** **Aspirin for Metabolic Dysfunction-Associated Steatotic Liver Disease without Cirrhosis: A Randomized Clinical Trial** Tracey G. Simon, MD, Assistant Professor, Medicine, Gastroenterology, Massachusetts General Hospital
3:10 PM – 3:25 PM	**Break**
3:25 PM – 3:50 PM	**Martin Prize for Clinical Research** **Genome Sequencing for Diagnosing Rare Diseases** Heidi Rehm, PhD, Professor, Pathology, Center for Genomic Medicine, Chief Genomics Officer, Massachusetts General Hospital
3:50 PM – 4:15 PM	**Martin Prize for Fundamental Research** **A T Cell-IL-3 Axis Controls Allergic Responses Through Sensory Neurons** Caroline L. Sokol, MD, PhD, Assistant Professor, Center for Immunology and Inflammatory Diseases, Massachusetts General Hospital
4:15 PM – 4:40 PM	**Martin Prize for Population Health Sciences** **Stepped Palliative Care for Patients with Advanced Lung Cancer: A Randomized Clinical Trial** Jennifer S. Temel, MD, Professor, Medicine, Hematology/Oncology, Massachusetts General Hospital

Floor Plan

Poster Sessions

Session 1: 10:00 AM – 11:15 AM

Session 2: 11:45 AM – 1:00 PM



Poster Listing by Category

Bioengineering & Devices

1 **Yuemeng Feng, PhD**
Spatial Resolution Evaluation of Dynamic Cardiac SPECT System: Simulation Study

2 **Jueun Jeon, PhD**
De novo designed nanobinders for improving protein biomarker analysis and therapeutic applications

3 **Francesca Marturano, PhD**
A Resistive Tapered Stripline (RTS) Technology to Enhance MRI Compatibility of Implantable Stimulators

4 **Uma Paithankar, BA**
Microfluidic capture of intact virus and cell-specific extracellular vesicles (EVs) from severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) patient biofluids

5 **Aashini Shah, BS**
Novel Plasmonic Nanocavity and Exciton Coupling-Based Implantable Aqueous Humor Sensors

6 **Alexandra Tautan, PhD**
Automatic estimation of frequency and spatial extent of rhythmic delta activity from EEG signals

Biomedical Imaging

7 **Sarah Altman, BS**
Progress Towards A 136 mT Portable MRI For Neonatal Brain Imaging

8 **Isaac Gallegos, BS**
Multi-Spectral NIR-II Photoacoustic Microscopy Utilizing Compact Custom All-Fiber Amplifier

9 **Jintaek Im, PhD**
Dynamic Subcellular Imaging with Spectrally Encoded Confocal Microscopy (D-SECM)

10 **Parisa Kaviani, MD**
Augmentation In Ai Models: Enhancing Radiology Impressions Through Comparative Validation, Prompt-Based Learning, And Rouge Evaluation

11 **Mehrbod Mohammadian, PhD**
Imaging the Role of Skull Bone Marrow Immunity in Chronic Low Back Pain: A Positron Emission Tomography Study

12 **Swarali Paranjape, MS**
Harvard Dots (H-Dots) as a Versatile Theranostic Platform for Image-Guided Surgery and Targeted Drug Delivery

13 **Shvan Raheem, PhD**
Claudin 18.2 as a biomarker for imaging and radioligand therapy of gastric and pancreatic tumors

14 **Michele Scipioni, PhD**
The Human Dynamic NeuroChemical Connectome (HDNCC) Scanner: A Brain-dedicated PET Scanner Integrated with the 7-T MRI Siemens Magnetom Terra

15 **Sergio Valencia, MD**
Time of Flight Magnetic Resonance Angiography at 7T: A Comparison with 3T

16 **Atsushi Yamashita, PhD**
Dual-Channel NIR Fluorescence Imaging with Indocyanine Blue and Indocyanine Green for Enhanced Intraoperative Surgical Guidance

Cancer

17 **Hazim Ababneh, MD**
5-5-5 ABRT (Adaptive Bridging Radiation Therapy) – Artificial Intelligence Enters the CAR (-T) in Relapsed/ Refractory Large B-Cell Lymphoma

18 **Derek Allen, B. Eng**
Photodynamic Therapy Stimulates the Immune System and Potentiates Immunotherapy in a Pancreatic Cancer Model

19 **Ezgi Antmen, PhD**
Heterogeneity of Circulating Tumor Cells: Understanding the Complex Biology of CTC-Immune Cell Hybrids

20 **Rami Awwad, BS**
Modulating PARP1 activity with Stearoyl-CoA desaturase to regulate DNA damage repair in GBM

21 **Jung Woo Bae, MS**
Pooled transcription factor overexpression screening uncovers novel regulators of chemoresistance in pancreatic ductal adenocarcinoma

22 **Mary Boulanger, MD**
Pilot Feasibility Trial of a Supportive Care Digital Application for Patients with Advanced Non-Small Cell Lung Cancer

23 **Riddha Das, PhD**
Engineering and Stimulation of Dendritic Cells for Cancer Immunotherapy

24 **Sayali Daware, BS**
Targeted Therapy with CDK4/6 Inhibitors in IDH-Mutant Gliomas

25 **Yohannes Gemechu, PhD**
A Novel Self-Assembling Vaccine, VTX-067, targeting E6/E7 proteins of Human Papilloma Virus Induces T Cell-Mediated Immune Responses and Inhibits Tumor Growth in a Murine Model of Cervical Cancer

26 **Demi Gerovasilis, BS**
Targeting the stem-like cell state in IDH-mutant gliomas with chimeric antigen receptor (CAR)-T cells

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27 **Alexander Jucht, MD**
Dissecting the metabolic heterogeneity of cell states in glioblastoma

28 **Hyung Shik Kim, PhD**
A ribonucleotide carbohydrate system (iRNC) enhances antigen presentation and controls glioblastoma

29 **Sophia Kovatsis, BS**
Targeting Cell States in Glioblastoma Organoid Models with Chimeric Antigen Receptor-T Cells

30 **Nicole Lester, BS**
Analysis of treatment-associated effects in matched pre- and post-treatment pancreatic ductal adenocarcinoma using whole transcriptome spatial molecular imaging

31 **Isabela Lima, MD**
Proton Beam Therapy for Advanced Periocular Skin Cancer: An Eye-Sparing Approach

32 **Jack Lu**
Evaluating a Highly Multiplexed Spatial Proteomics Platform to Study Tumor Immune Interactions in Glioblastoma

33 **Niamh McNamee, PhD**
Transcription factor TP63 is involved in metabolic programming in esophageal cancer

34 **Olivia Mooradian, BS**
Synergistic Effect of Minocycline and Photodynamic Priming in the Treatment of Pancreatic Ductal Adenocarcinoma

35 **Amaya Pankaj, MBBS**
Intraductal Papillary Mucinous Neoplasm Cellular Plasticity linked with Repeat Element Dysregulation

36 **Kishwor Poudel, PhD**
Tailored Hybrid Biomimetic Nanovaccine (HBNV) for KitK641E-Mutant Melanoma: Fabrication, Functional Validation, and Immunotherapy Reinvigoration

37 **Bethany Rothwell, PhD**
Proton Flash-Arc Therapy (PFAT): A Novel Approach for Cancer Radiotherapy

38 **Roshni Sarathy, BA**
Interventions to Manage Fear of Cancer Progression for Patients with Advanced Cancer: A Systematic Review.

39 **Jacob J. Smith, BSc**
Deep Profiling of Immune Reconstitution Following Radiation Treatment for Oligometastatic Prostate Cancer Identifies Immune Signatures Associated with Recurrence

40 **Victor V. Onecha, PhD**
In-Vitro Modeling of Cellular Response to Radiation in Radiopharmaceutical Therapy Experiments

41 **Isabella Vianna, MA**
Changes in one-carbon metabolism mediate late recurrence in hormone receptor-positive breast cancer

42 **Shivendran Vytheswaran, BS**
Photodynamic Therapy-Induced Immunogenic Cell Death in a 3D Heterotypic Pancreatic Tumor Spheroid Model and its Potential in Enhancing Response to Anti-PD-1 Treatment

43 **Sarah Waliany, MD, MS**
Mechanisms of resistance to first-line vs later-line alectinib in ALK-positive NSCLC

44 **Chen Wang, MD, MS**
Ultra-processed food and risk of early-onset colorectal cancer precursors among women: A prospective US cohort study

45 **Chun Wai Wong, PhD**
Defining the mechanisms and interactions of chemotherapy and immunotherapy in lung cancer

46 **Erika Yamazawa, MD, PhD**
Preclinical investigation of a novel brain penetrant combination therapy targeting RAF and MEK for melanoma brain metastasis

Cardiovascular

47 **Jan Michael Brendel, MD**
Sex-specific Prognostic Value of Quantifying Coronary Plaque in Patients with Stable Chest Pain

48 **Anna Demelo, BS**
Sex-Based Outcomes in HeartMate 3 (HM3) Left Ventricular Assist Device (LVAD) Support

49 **Takenori Ikoma, MD, PhD**
Obese HFpEF Patients Exhibit Distinct Augmentation Patterns of VO2 Components During Exercise

50 **Utarat Kaewumporn, MD**
Potential Role of Spectral Chest X-ray as a Screening Test for Coronary Artery Disease

51 **Isabela Landsteiner, MD**
Comprehensive Mapping of Exercise Hemodynamic Responses and Multi-Organ System Reserve Capacity in HFpEF

52 **Daniel Oo, BA**
Opportunistic Assessment of Cardiovascular Risk using AI-Derived Structural Aortic and Cardiac Phenotypes from Non-Contrast Chest Computed Tomography

53 **Bronwen Rees-Wiedemann, BA**
Impact of concomitant surgery on left ventricular assist device (LVAD) outcomes

Poster Listing by Category

54 **Madhu Singh, BA**
Plasmalogen Control of Peroxisome Degradation Confers Protection from Ischemia

55 **Carly Steifman, BA**
Endothelial cell dysfunction is detected in children with long COVID

56 **Xiao Xiao, MS**
Epitranscriptional Regulation by METTL3 Protects Against Heart Failure with Preserved Ejection Fraction

Child and Adolescent Health

57 **Olivia Dinwoodie, PhD**
Understanding the Role of Compression and Inflammation in the Formation of Pulmonary Hypoplasia Induced by Congenital Diaphragmatic Hernia

58 **Sujata Tewari, BA**
Projecting lifetime HIV-related healthcare costs for youth with HIV in the United States

59 **Marielena Trujillo, BS**
Targeted Physical Activity Intervention to Decrease PCOS Risk in Girls: A Pilot Study on Feasibility and Timing of Intervention

60 **Dongmei Zhi, PhD**
Unravelling Polygenic Risk and Environmental Interactions in Adolescent Polysubstance Use: a U.S. Population-Based Observational Study

Computational/Bioinformatics, AI

61 **Yigeng Cao, MD**
Precision timing and dosing of preemptive add-on prophylactic medication against severe acute graft-versus-host disease: a prospective interventional trial of a machine learning model

62 **Jingya Cheng, MS**
Temporal Learning with Dynamic Range (TLDR) for multi-exposure, multi-treatment event predictions in electronic health records

63 **Nicolo Cogno, PhD**
A mechanistic model of brain necrosis progression based on vascular heterogeneity

64 **Lauren Cooke, MS**
RoentMod: Synthetic Pathology on Chest X-Rays Reveals Potential for Bias in Image Interpretation Models

65 **Julia Geller, BS**
A Novel Application for Evaluating Treatment Efficacy in ALS Using Real-World Data

66 **Paola Lopez Zapana, PhD**
Markov Field Network Model of BMI-Driven Protein Networks and Preterm Birth Subtypes in 2nd Trimester Cohorts

67 **Charles Lu, BA, BS**
Using Large Language Models to identify cutaneous immune-related adverse events in response to immunotherapy.

68 **Pawel Renc, MS**
Adaptive Risk Estimation System (ARES): A Next-Generation Early Warning System for Real-Time Patient Care

69 **Patrick Salome, PhD**
AI & Big Data in MRI: A Dual Study on Image Classification and Intensity Normalization for Brain Imaging

70 **Jiazi Tian, MS**
An Agentic AI Workflow for Detecting Cognitive Concerns in Real-world Data

71 **Yilun Wu, MS**
A natural language processing algorithm accurately classifies diverticulitis and associated complications and predicts the risk of long-term outcomes

Endocrinology

72 **Thomas Bitar, BS**
Lower oxytocin levels are associated with increased anxiety and depressive symptoms in adults with obesity

Genetics & Genomics

73 **Brigitte Demelo, BA**
'LOMARS' Missense Mutation Rescues the Huntingtin Null Allele in Mice

74 **Michael Fallon, BA**
Improving the Precision of Single Base Genome Edits with Engineered CRISPR Base Editors

75 **Paula Hornbostel, BS**
Biomarkers for Somatic Instability of the CAG Repeat in Huntington's Disease

76 **Maria Iorini, BS**
Using Polygenic Risk Scores to Predict Risk of Attention-Deficit/Hyperactivity Disorder and Disruptive Behavior in Youth

77 **Jasbeer Khanduja, PhD**
lncRNA-Mediated Heterochromatin Assembly

78 **Ka Ying Toby Law, MA**
Capturing time-varying childhood adversity exposures through DNAm profile scores to predict adulthood depressive symptoms

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79 **Esaria Oliver, BS**
CRISPR-Cas9-mediated Msh3 knockout in mice to assess impact on Huntington's disease phenotypes and therapeutic implications

80 **Paolo Pigini, PhD**
Defining the Landscape of Poison Exon Splicing Events in the Human Brain: Implications for Neurodevelopmental and Neurodegenerative Disorders

81 **Shota Shibata, MD, PhD**
PMS1 as a potential therapeutic target for Huntington's Disease

Health Disparity and Health Equity Research

82 **Victoria Cameron, BS**
The Association of Food and Housing Insecurity and Resource Placement in Boston

83 **Pragya Dhar, MPH**
Leveraging a Quality & Safety Continuous Process Improvement Framework to Address Disparities in Breast Cancer Screening

84 **Maria Galvez, BA**
Rates of retention among underrepresented minoritized groups in Alzheimer's Disease research; findings from the Longitudinal Cohort at MADRC

85 **Mariam Kapanadze, MPH**
Strategies for Academic and Leadership Advancement among Women in Emergency Medicine

86 **Patrisha Lazatin, MD, MS**
Evaluating differential referrals occurring in the Tourette Syndrome Center of Excellence Clinic, Mass General Brigham: A cross-sectional study

87 **Christine Li, BS**
Evaluating the impact of community-based dermatology education on health-seeking behaviors among persons experiencing homelessness

88 **Hesam Mahmoudi, PhD**
Uncovering Gaps in Modeled Smoking Histories: Implications for Lung Cancer Screening Eligibility

89 **Jordyn Morey, BS**
Results From a Qualitative Study of Race and Ethnicity Data Collection in the Emergency Department

90 **Marine Nimblette, BS**
The Role of Transnational Families and the Asylum Process among U.S. Asylum Seekers

91 **Dylan Norton, BA**
Geospatial Analysis of Penicillin Allergy De-Labeling

92 **Jake Nusynowitz, BS**
Assessing the influence of socioeconomic factors on transgender patients with hidradenitis suppurativa

93 **Keity Okazaki, MD**
Racial and Ethnic Disparities after Hip Fracture in Older Adults with Type 2 Diabetes

94 **Adriana Araceli Rodriguez Alvarez, MD**
Sex-based differences in clot strength among patients with peripheral artery disease receiving antiplatelet treatment

95 **Lana Sabbah, MA**
"I'm sorry, I can't hire you because of that": Examining the role of employment and exclusion on health and well-being among U.S. Asylum Seekers

96 **Santiago Saldivar, BA**
From Community to Commencement: Analyzing the Correlation Between Social Capital Variables And Graduation Rates Among United States High Schools

97 **Ruchi Shah, MD**
Penicillin Allergy De-Labeling Disparities in Gender Marginalized Groups

Immunology/Inflammation

98 **Bryan Alvarez-Carcamo, BA**
Neutrophil Inflammation as a Key Driver in Pediatric Post-Acute COVID-19 Syndromes

99 **Maria Carolina Avenatti, MD**
Role of Proton-Secreting Epithelial Cells in Shaping Urogenital Tract Mucosal Immunity

100 **Edward Chen, BS**
Investigating the Effect of Type 2 Inflammation on Dynamic Secretory Cell Antigen Passaging

101 **Sheng-Yin Chen, MD, MPH**
Association of Distinct Microbial and Metabolic Signatures with Microscopic Colitis

102 **Sophia Feinerman, BA**
Enhanced placental antibody transfer efficiency with longer interval between maternal respiratory syncytial virus vaccination and birth

103 **Lilah Gmyrek**
Lipid metabolic pathways linked to STING signaling and interferon-B gene induction in macrophages and dendritic cells

104 **Ninghui Hao, BS**
Somatic variant predictors of cutaneous immune-related adverse events in cancer patients treated with immunotherapy

105 **Koki Hayashi, PhD**
Defensive tolerance drives the reprogramming and dysfunction of infiltrating pathogenic B cells resulting in the promotion of tolerance

Poster Listing by Category

106 Laura Ibanez-Pintor, MD
Sex differences in cord blood inflammation at birth in offspring exposed to gestational diabetes mellitus

107 Jenna Lancey, BA
Fgl2 is an immunomodulatory molecule that is upregulated in tolerant kidney graft recipients

108 Owen Martin, BA
Single-cell atlas of human liver and blood immune cells across fatty liver disease stages reveals distinct signatures linked to liver dysfunction and fibrogenesis

109 Tomer Milo, PhD
A paradox of foreign-reactive regulatory T cells and a proposed resolution by a lymph node microdomain theory

110 Sergio Monares, MD
RSV Immunoprophylaxis in Infants and Breakthrough Infection: Clinical Impact and Viral Features

111 Marielos Posada Posada, MD
Impact of Semaglutide Use in Obese and Diabetic Patients with Hidradenitis Suppurativa

112 Jiaxian Shen, PhD
Perturbed Gut Viral Ecology in Inflammatory Bowel Disease: A Multi-cohort Study

113 Maxwell Song, BA
Defining Disease-Specific Epithelial Cell Phenotypes in Thyroid Autoimmunity

114 Alice Emma Taliento, PhD
Multiple subsets of T helper 2 lung-resident memory cells are established in a mouse model of allergic inflammation

Infectious Disease

115 Sophia Ahn, BA
The Role of Gut Microbiota on Cardiovascular Disease Progression for People with HIV

116 Natalie Eidenschink, BA
Superhydrophobic Bandages and Antimicrobial Photodynamic Therapy as an Innovative Approach to Tackle Third-Degree Burn Infections In Vivo

117 Owen Glover, BA
Investigating Shifts in Viral Entry of Emerging SARS-CoV-2 Variants

118 Xuan Guo, MS
Presentation of RhCMV 68-1 vaccine-identified SIV epitopes by human and rhesus MHC-E

119 Mansi Gupta, BS
Exploring the PREVENT HF Score and Myocardial Function among Persons with HIV

120 Chia Jung Li, PhD
Epitope-Driven Effector Functions of Broadly Neutralizing Antibodies Across Diverse HIV Isolates: Insights for Next-Generation Therapeutics

121 Tristan Lim, MD, MS
Multi-agent immunosuppressive therapy for immune-related adverse event (irAE) treatment is associated with high rates of infectious complications

122 Mri Mandal, BS
Developing Viral Culture and Quantification Protocols to Assess Infection Dynamics of RSV and Influenza

123 Adam Nitido, PhD
Error Rate of Replication Sequencing (ERR-Seq) Reveals High Mutation Rate Variation Within and Across HIV-1 Strains

124 Nartsav Omur, BA
ERR-Seq 2: HIV-1 Mutation Rate Measurement Using Long-Read Sequencing

125 Hemi Park, MPH
Plasma Neurofilament Light Chain Suggests Advanced Neuronal Age in Cognitively Unimpaired People with HIV on Antiretroviral Therapy in ACTG A5322 (HAILO)

126 Le Anh Thu Pham, MS
Activation of Virulent Secretion System in Shigella

127 Volney Spalding, BS
Exposure of HIV envelope protein gp120 alone modulates hepatocyte dynamics and signaling.

128 Jean Trinidad-Rivera, BS
Degradable Transgene via Modification of a Cre-Lox Recombination System as Regulatable Gene Therapy Vector

129 Hamid Reza Zarei, PhD
Modeling the Value of Information and Implementation of a Study on HIV Pre-exposure Prophylaxis (PrEP) Toxicities Among Adolescents in the United States

Neurosciences

130 Luca Angeleri, BS
Radiomics Derived Brain Age Influences Patient Reported Outcomes After Acute Ischemic Stroke

131 Sandeep Aryal, PhD
RANBP1 causes splicing-independent STMN2 loss in TDP-43 proteinopathy

132 Alexander Atalay, BA
Integrating Effective and Structural Connectivity in the Human Brain

133 Izabella Bankowski, BS
Maternal TLR7 activation induces maternal autoimmunity, resulting in male-biased immune and ASD-like behavior alterations

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134 Evelyn Barringer, BS
Dynamic pupillometry and live neutrophil function in infection-associated chronic conditions (IACC)

135 Celia Bianco, BS
Neuropathological Correlates of Plasma GFAP Levels in Alzheimer's Disease and Related Dementias

136 Adel Boudi, PhD
Characterizing the Role and Mechanisms of Gene Fusion in Amyotrophic Lateral Sclerosis

137 Ayleen Castillo-Torres, BA
Measuring phosphorylated tau as a biomarker for amyotrophic lateral sclerosis

138 Siwei Chen, PhD
Cellular Mechanisms of Early Brain Overgrowth in Autistic Children: Elevated Levels of GPX4 and Resistance to Ferroptosis

139 Joshua Chun, BS
Post-translational Modification Mimetics of Tau Reveal Patterns Of Aggregation And Liquid-liquid Phase Separation

140 Maria Camila Cortes Albornoz, MD
Normal Development of the Fetal White Matter Crossroads

141 Julie DiCarlo, MS
The role of cognitive function in upper extremity motor impairments after stroke

142 Anna Du, BA
Transcranial Magnetic Stimulation Improves Brain Network Functional Connectivity in a patient with Posterior Cortical Atrophy

143 Alex Dyson, PhD
MEK Inhibition as a Potential Therapeutic Strategy for the Non-Tumor Manifestations of Neurofibromatosis Type 1 (NF1)

144 Simon Ehricke
Tau's Dual Role: Alzheimer's Disease by Antimicrobial Defense

145 Ava Farnan, BA
Portable, Low-Field MRI for Alzheimer's Disease: Detecting Patterns of Atrophy Using Machine Learning

146 Jake Galler, BS
Short-interval common game play distinguishes people with and without cognitive impairment

147 Aarushi Gandhi, BS
Investigating Blood-Brain Barrier Functionality in ACTA2 Multisystemic Smooth Muscle Dysfunction Syndrome (MSMDS)

148 Julianna Gerold, BA
Improving journal author guidance to address ethical challenges in the utilization of race and ethnicity population descriptors in human neuroscience research

149 Nika Ghavamizadeh, BA
Modeling Brain State Dynamics in Older Adults: A Hidden Markov Model Approach

150 Alkis Hadjiosif, PhD
Can subscales of the upper-limb Fugl-Meyer assessment provide evidence for competition between descending motor tracts after stroke?

151 Bruno Hammerschlag, BS
Dried blood spots as a matrix for measuring AD biomarkers: optimizing parameters of analysis and evaluating technical stability

152 Firdaus Fabrice Hannanu, MD, PhD
Changes in Choroid Plexus Sub-Compartments in Aging and Premanifest Synucleinopathy Using High-Resolution 7 Tesla Structural and Functional MRI

153 Alexander Hary, BS
Locus coeruleus tau validates and informs high-resolution MRI in aging and at earliest Alzheimer's pathology stages

154 Bing He, PhD
Association between basal forebrain network connectivity and cognition in preclinical autosomal dominant Alzheimer's disease

155 Andrew Iwanowicz, BS
Lipidomic surveys in plasma reflect genotype and therapy dependent changes in striatum in a Huntington's disease mouse model

156 Kristy Jay, PhD
Functional analysis of O-GlcNAc in sleep and circadian rhythm in Drosophila

157 Arp-Arpa Kasemsantitham, BA
Damage to rich-club organization is related to clinical, but not patient reported outcome measures in acute ischemic stroke

158 Eugene Kim, BS
Fibrin(ogen) accelerates inflammatory-mediated vascular remodeling in a mouse model of cerebral amyloid angiopathy

159 Grace Levine, BA
Assessing the Efficacy of The NIH Toolbox to Characterize Executive Functioning Deficits in Autistic Individuals

160 Adrian Lin
Variability in Muscle Co-activation Patterns Within Upper Extremity Fugl-Meyer Sub-Scores After Stroke

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161 **Erik Lindgren, MD, PhD**
Impact of Modifiable Risk Factors on Neuroimaging Markers of Brain Health in Acute Ischemic Stroke

162 **Fleur Lobo, PhD**
A novel brain-permeable HDAC11-selective inhibitor significantly reduces AD neuropathology in a Tau P301S mouse model.

163 **Ekim Luo, PhD**
Neuroinflammation in the Primary Somatosensory Area is associated with Pain Widespreadness in Individuals with Chronic Low Back Pain

164 **Vincent Malotaux, PhD**
Distinct early cortical thickness patterns in heterozygous APOE3-Christchurch carriers and age-matched controls

165 **Md Mahfuz Al Mamun, PhD**
Transcriptomic Signatures of ASD Risk Genes Uncover Molecular Convergence in Idiopathic Autism

166 **Torrey Mandigo, PhD**
Drosophila modeling of insomnia- and cardiovascular disease-associated genes finds excessive sleep correlates with aberrant cardiac function

167 **Ranee Zara Monsanto, MD, MS**
Unraveling the inflammatory landscape in X-linked dystonia parkinsonism

168 **Wadzanai Ndambakuwa, BA**
Neuroinflammation alters neuronal activity in an experimental model of multiple sclerosis

169 **Hannah Nemeth, BA**
Impact of Lifetime Estradiol Exposure on Memory Function in Midlife Women

170 **Divya Patni, PhD**
Blocking RAN translation without altering repeat RNAs rescues C9ORF72- related ALS/FTD phenotypes

171 **Nandini Ramesh, PhD**
Genetic and pharmacological inhibition of PKC alleviates nucleocytoplasmic transport disruption in FUS-mediated ALS

172 **Charles Jourdan Reyes, PhD**
X-linked dystonia-parkinsonism is a novel genetic four-repeat tau astrogliopathy

173 **Riannon Robertson, BA**
Lipid droplet dynamics in Huntington's Disease

174 **Johanna Rotta, MD**
Arteriolosclerosis in Patients with Cerebral Amyloid Angiopathy - an MRI and Histopathological Study

175 **Christopher Simon, PhD**
Elevated TDP-43 serum levels associated with postoperative delirium following major cardiac surgery

176 **Dhanush Sivasankaran, BS**
Identifying Tau proteopathic species isolated from Alzheimer's disease brains

177 **Martin Sjoegaard, MS, PhD**
Hippocampal ripples predict motor learning during brief rest breaks in humans

178 **Maggie Slamin, BS**
Microglial Estrogen Receptors Program Male-Biased Vulnerabilities to Perinatal Challenges

179 **Emma Spooner, BS**
Parafoveal macular thinning and Alzheimer's disease risk in healthy midlife adults dependent on sex

180 **Catarina Tristao-Pereira, PhD**
Association among cerebral glucose metabolism, mild behavioral impairment and cognition in autosomal-dominant Alzheimer's disease

181 **Işıl Uluç, PhD**
Look There: A Study of Cerebellar Involvement in a Visually-Guided Saccade Task using MEG

182 **Hilde van den Brink, PhD**
In vivo imaging of gadolinium-based contrast agent leakage in patients with cerebral amyloid angiopathy

183 **Kali vom Eigen, BA**
Vasomotion patterns in the visual cortex of mice undergoing high-frequency 40Hz visual stimulation

184 **Aditii Wakhlu, BS**
Sex Effects of Respiratory-Gated Auricular Vagal Afferent Nerve Stimulation (RAVANS) on the Regulation of the Central Autonomic Network in Major Depression

185 **Anat Weiss Sadan, MHA**
Optimizing Study Startup Timelines in an Externally Funded Multiple Site Expanded Access Protocol for ALS participants at MGH

186 **Seda Yasa, PhD**
Addressing Microglial Dysfunction in the CLN3-Related Lysosomal Disease

187 **Jessica Yeager, BA**
Detecting Covert Consciousness and Predicting Recovery after Severe Brain Injury: COMPASS Study Protocol

188 **Da Zhi, PhD**
Systematic comparison of resting-state vs. task-based brain parcellation for precision functional mapping

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Orthopedics/Sports Medicine

189 **Srish Chenna, BSE**
Acetabular Labral Tear Size as a Predictor of Long-Term Outcomes and Conversion to Total Hip Arthroplasty: Minimum 8 Year Follow-Up

190 **Muhammad Hamza Ilyas, MD**
Machine Learning Models Predict Pulmonary embolism in Patients Undergoing Total Hip Arthroplasty: An ACS-NSQIP Database Analysis

191 **Gabriel Moraes de Oliveira, MD**
The influence of graft choice on quadriceps strength after ACL reconstruction

192 **Jeffrey Mun, BA**
Minimum 5-Year Outcomes of All-Arthroscopic Capsular Autograft Hip Labral Reconstruction

193 **Atta Taseh, MD**
The Relationship Between Foot Muscle Characteristics and Falls: An MRI-Based Evaluation

194 **Abigail Tianai Zhang, MS**
Automated Readmission Prediction in Spine Oncology: A Natural Language Processing Approach to Clinical Documentation

195 **Serafina Zotter, BS**
Clinical Outcomes of MPFL Reconstruction in Pediatric Patients with First-Time Versus Recurrent Patella Dislocations: A Cohort Comparison

Population, Health Care Delivery, and Global Health Research

196 **Sarah Anwar, BS**
Strengthening Healthcare Training for Skin-Related Neglected Tropical Diseases: Addressing Gaps and Expanding Access

197 **Grace Bizup, BA**
Psychological Distress is Prevalent and Interdependent Among Patients with Decompensated Cirrhosis and Their Caregivers

198 **Ethan Borre, MD, PhD**
Value of an implementation trial on long-acting antiretroviral therapy for US persons with persistent HIV viremia

199 **Zachary Chau, BS**
A preliminary cryopreservation protocol for Anopheles mosquito larvae

200 **Anushka Dalvi, BS**
Prognostic Communication, Symptom Burden, Psychological Distress, and Quality of Life Among Patients with Decompensated Cirrhosis

201 **Julie Deleger, BA**
Cost-Effectiveness of Community Tuberculosis Screening in South Africa

202 **Madelyn Eippert, BA**
Application of the Health Belief Model to Penicillin Allergy-Related Belief Patterns

203 **Jennifer Hebert, BS**
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Bioengineering & Devices

POSTER NUMBER:
1

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Spatial Resolution Evaluation of Dynamic Cardiac SPECT System: Simulation Study

Investigators: Y. Feng, M. A. Kupinski, M. P. Ottensmeyer, W. Worstell, L. R. Furenlid, H. Sabet

The authors acknowledge financial support of the NIH Grant No. R01HL145160

A dynamic cardiac SPECT (DC-SPECT) system is under development at the Radiation Physics and Instrumentation Laboratory. SPECT is a medical imaging technique that uses radionuclides for non-invasive imaging of targets within the human body and can provide functional imaging of organs. Recent advancements in cardiac-dedicated SPECT systems have improved the diagnosis of cardiac diseases such as coronary artery disease. Improving sensitivity and imaging resolution remain ongoing challenges in instrument development. We aim to develop a cardiac-dedicated SPECT system that offers high sensitivity and high imaging resolution, thereby reducing scanning time or the required injected dose while providing high-resolution dynamic cardiac imaging.

This work presents an accurate analytical approximation of the solid angle for list-mode maximum likelihood expectation maximization (MLEM) reconstruction, specifically tailored to the geometry of DC-SPECT, which features fixed detectors forming a C-shape similar to the human torso and uses pyramid-shaped collimators. The system's sensitivity and spatial resolution are assessed using Monte Carlo simulated data. The reconstructed spatial resolution is evaluated through both the proposed analytical calculation and simulation-based methods. Point sources, line sources, a Derenzo phantom, a Jaszczak phantom, and an XCAT cardiac phantom were simulated and reconstructed. Our results indicate that, with the current system design, DC-SPECT achieves a resolution of 5.5 mm for hot regions and 6.0 mm for cold regions at a sensitivity of 0.07% over a 15 cm diameter spherical field of view. The reconstruction methods successfully recovered myocardium voxels in a 5-minute acquisition, demonstrating the potential of the DC-SPECT system for cardiac imaging.

POSTER NUMBER:
2

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De novo designed nanobinders for improving protein biomarker analysis and therapeutic applications

Investigators: Y. Choi, I. Barth, H. Woo, H. Lee

The precise analysis of protein biomarkers is crucial for the investigation of extracellular vesicles and their clinical applications. Although antibodies are commonly employed for this purpose, their inherent limitations, such as cross-reactivity and inconsistent affinity, compromise the reliability of assays. In this study, we present computationally designed nanobinders (DNBs) as a viable alternative affinity ligand for the analysis of proteins in extracellular vesicles. Utilizing a machine learning-based approach for de novo protein design, we established a computational framework aimed at optimizing the specificity of DNBs, which we subsequently validated through in vitro assays. Here, a DNB, which is targeting programmed death-ligand 1 (PD-L1) as a proof-of-concept, exhibited significant performance compared to conventional antibodies, achieving signal intensities in cellular imaging that were up to 51 times stronger, alongside improved sensitivity in the analysis of extracellular vesicles. Furthermore, this DNB effectively inhibited immune checkpoints, highlighting the potential of DNBs as a promising platform for both diagnostic and therapeutic applications.

Bioengineering & Devices

POSTER NUMBER:
3

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A Resistive Tapered Stripline (RTS) Technology to Enhance MRI Compatibility of Implantable Stimulators

Investigators: F. M. Marturano, I. A. Ay, G. B. Bonmassar

Implantable stimulators, such as those used in deep brain stimulation (DBS), remain incompatible with full MRI use due to the presence of extension leads containing internal metal microwires. These wires pose significant safety risks, including RF-induced heating, which limits MRI accessibility for patients with these implants. To address this challenge, we developed and tested a Resistive Tapered Stripline (RTS) design for new generation DBS lead microwires. This innovative approach involves creating a sharp interface between two thin metal layers that is able to reflect undesired radiofrequency (RF) currents back to the pulse generator. This mechanism substantially reduces RF-induced heating while preserving essential electrical conductivity.

Thin films of titanium and gold were deposited onto a non-conductive, non-magnetic microwire substrate using physical vapor deposition, optimizing the design for both electrical performance and biological safety.

To ensure biocompatibility, the selected materials were evaluated according to ISO 10993-6 guidelines in a rodent study. Brain tissues from rats implanted with RTS wires and commercially available control leads were analyzed microscopically 35 days post-implantation, assessing microgliosis, astrocytosis, neurodegeneration, and demyelination. No significant differences were observed between RTS and control leads across these endpoints, confirming the biocompatibility of the proposed RTS design.

The RTS technology marks a transformative advancement in implantable stimulator design, enabling safe MRI use while maintaining long-term functionality and meeting rigorous biocompatibility standards. Beyond DBS, this versatile materials and manufacturing approach has the potential to enhance the safety and performance of other chronically implantable devices, such as cardiac pacemakers and spinal cord stimulators.

Bioengineering & Devices

POSTER NUMBER:
4

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Microfluidic capture of intact virus and cell-specific extracellular vesicles (EVs) from severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) patient biofluids

Investigators: U. K. Paithankar, D. C. Rabe, A. Choudhury, D. Lee, E. G. Luciani, U. K. Ho, C. Dymond, M. B. Goldberg, P. S. Lai, G. M. Boland, J. F. Wise, S. L. Stott, Mass General Brigham Biobank

There has been a growing interest in the study of cell type-specific extracellular vesicles (EVs). The exact roles that these EV populations play in health and disease are still being explored, but their importance for targeted cell-specific communication is clear.

Recent studies have utilized techniques such as immunocapture to isolate cell-specific EVs. In COVID patients, still others have employed methods to isolate bulk EVs from patient plasma. Our microfluidic setup employs affinity capture to isolate multiple cell-specific EV populations from COVID patient plasma. This creates a unique opportunity to isolate these multiple distinct signals from a single timepoint for a given patient's liquid biopsy.

The present study aims to enhance our understanding of how we may be able to track COVID patient prognosis, as well as identify potential biomarkers to give insight into patient needs in a clinical setting.

Here we show the successful serial microfluidic capture and subsequent RNA-sequencing of cell-specific EV populations from COVID patient plasma. Further, we captured intact virus to quantify each patient's timepoint-specific viral load. We devised a bioinformatics pipeline for filtering our EV RNA-sequencing data to conduct downstream analyses. Differential gene expression analyses yield significant genes (by adjusted p-value and log-fold-change) for several comparisons across patient infection severity and viral load. Notably, as patient severity increases, in innate immune EVs we see an upregulation of genes involved in: RNA-binding, mitochondrial, and protein ubiquitination activities.

We hope to derive insights for future pandemics as well as explore the potential for tracking long-COVID patient conditions.

Bioengineering & Devices

POSTER NUMBER:
5

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Novel Plasmonic Nanocavity and Exciton Coupling-Based Implantable Aqueous Humor Sensors

Investigators: A. S. Shah, A. Garg, E. I. Paschalis, L. F. Tadesse

Visual impairment due to Age-related Macular Degeneration (AMD) affects nearly 20 million adults in the United States annually, 196 million globally, and directly increases in prevalence with ageing populations. There is no process to continuously and in vivo monitor biomarkers for AMD without frequent visits to the ophthalmologist. Tear film is ultrafiltered and a poor proxy for immune monitoring, but syringe-based biopsies pose high risks for infection and structural damage. However, cataract surgery, which is performed on >4 million adults in the US annually, already inserts an artificial lens (IOL) into the anterior chamber, into which we can embed plasmonic nanocavity biosensors that detect selected immune markers at a sensitivity of 10^(-16) g/ml using a patent-pending plasmon-exciton coupling-based sensing approach. DNA-based capture agents will change conformation upon target binding, placing nanoclusters inside plasmonic nanocavities, taking advantage of Rabi splitting in light-matter hybrid states and paving the way for single-molecule sensitivity. Using Finite Difference Time Domain simulations, we optimized the gap thickness and mode nature of gold-silica-gold plasmonic nanocavities, achieving ~1000 nm^3 magnetic dipole mode volumes. With semi-classical simulations, plasmonic nanocavities showed a spectral split of 175 nanometers in the presence of a single nanocluster, indicating the potential for single-molecule sensitivity. During fabrication, we optimized lithography and etching protocols to precisely align the magnetic dipole mode with the absorption band of the excitonic particles and achieve agreement with the simulation results. Future research will include engineering the capture probes to validate the sensor's limit of detection for selected immune markers.

POSTER NUMBER:
6

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Automatic estimation of frequency and spatial extent of rhythmic delta activity from EEG signals

Investigators: A. M. Tautan, J. Jing, B. Westover, S. Zafar

Rhythmic delta activity (RDA) is an abnormal EEG rhythm on the ictal-interictal continuum (IIC). RDA at higher frequencies in either its lateralized (LRDA) form presents a greater risk for future seizures and is linked to increased mortality and disability.

Purpose: This work proposes methods for estimating the frequency and spatial extent of RDA, both generalized and lateralized, based on signal frequency analysis. Automatic methods would decrease the physician burden of manual annotation, while also facilitating retrospective studies on large amounts of data.

Methods: Three frequency-based RDA detection methods are proposed on 10 second EEG segments: (i) oscillation modelling based on Fourier Transform; (ii) enhancement of the Fourier based algorithm with variance-based channel selection; (iii) detection based on Hilbert-Huang Transform. The results were evaluated by comparing the output of the algorithms with the frequency and spatial extent annotations of an experienced clinical neurophysiologist on LRDA and GRDA segments.

Results: A total of 210 LRDA and 285 GRDA EEG segments were annotated. All algorithms showed a high performance when compared to the expert annotations. The smallest mean squared error (MSE) for the event frequency was of 0.20Hz and 0.15Hz for LRDA and GRDA respectively, while the smallest MSE for spatial extent was of 0.23 and 0.15 for LRDA and GRDA respectively, with 0 representing no channels affected and 1 a generalized RDA.

Conclusions: The automatic estimation of RDA frequency and spatial extent demonstrated excellent performance against expert annotations, enabling large-scale cohort studies on IIC EEG data and outcomes research.

Biomedical Imaging

POSTER NUMBER:
7

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Progress Towards A 136 mT Portable MRI For Neonatal Brain Imaging

Investigators: S. E. Altman, M. Sliwiak, D. Gupta, A. R. Purchase, J. Short, M. Davids, V. Klein, S. Bates, J. Stockmann, L. L. Wald, C. Z. Cooley

Neonates are particularly susceptible to Hypoxic-Ischemic Encephalopathy, a dangerous condition resulting from inadequate cerebral perfusion (HIE). Detection and monitoring of HIE is of utmost importance, necessitating diagnostic and prognostic neonatal brain imaging. However, transfer to conventional MRI scanners is infeasible for unstable pre-term neonates and their equipment, underscoring a need for NICU-compatible point-of-care MRI scanners. To this end, our team is developing a lightweight, portable 136 mT MRI scanner for bedside imaging, prioritizing minimal disruption to NICU care. The MRI scanner construction is underway. For the main magnet design, Finite Element Method magnetostatics simulations were performed to enable demagnetization-effect modeling. Genetic algorithm optimization was employed to target high field homogeneity over a 14 cm DSV for neonatal brain imaging. The resultant 18-ring Halbach array design, comprised of 1,848 NdFeB magnets, achieved a simulated mean field strength of 136 mT and inhomogeneity of 557 ppm over the 14 cm DSV. Gradient coils were designed to achieve at least 20% linearity within a 20 cm DSV at the magnet's isocenter using a BEM-SF method. The magnet was constructed using HDPE former rings and PLA spacers, aligned with threaded rods, and coaxially compressed utilizing jacks and flange nuts. Upon construction, field mapping revealed a mean field strength of 136 mT and inhomogeneity of 5,374 ppm over a 14 cm DSV pre-shim. Current efforts include passive shimming to improve magnet homogeneity, gradient coil construction and testing, RF and EMI hardware development, DWI pulse sequence design, powered cart construction, and validation with phantom testing.

POSTER NUMBER:
8

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Multi-Spectral NIR-II Photoacoustic Microscopy Utilizing Compact Custom All-Fiber Amplifier

Investigators: I. Gallegos, S. Bak, H. Lee, D. Veysset, B. E. Bouma

Near-Infrared-II (NIR-II) photoacoustic imaging offers a promising approach for label-free deep tissue imaging, enabling the visualization of endogenous species such as lipids and collagen. These biomolecules have significant roles in disease metabolism and can serve as valuable biomarkers. Conventionally, photoacoustic systems typically rely on high pulse energy and low repetition rate light sources, but recent advancements have led to the development of high-speed, clinically viable light sources based on stimulated Raman scattering (SRS). These novel sources can achieve optical excitation in the NIR-II window around 1200 nm, matching the second overtone of C-H bonds, with > 100 kHz repetition rates and pulse energies in the μJ range. These optical systems offer deep penetration depth leveraging reduced water absorption and tissue scattering, making them particularly relevant for clinical applications. We present a preliminary study that uses a custom-built nanosecond SRS fiber amplifier to perform multi-spectral photoacoustic imaging of various endogenous species. Using a photoacoustic microscope, we demonstrate spectral discrimination of lipids and collagen with relevance to prostate cancer biopsy guidance. Importantly, we foresee that the compact and affordable design of the light source will promote the dissemination of photoacoustic imaging as a powerful tool for detecting and studying disease-related biomarkers.

Biomedical Imaging

POSTER NUMBER:
9

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Dynamic Subcellular Imaging with Spectrally Encoded Confocal Microscopy (D-SECM)

Investigators: J. Im, H. Hinnerk, J. Kim, G. J. Tearney

We acknowledge the John and Dottie Remondi Family Foundation for their generous support of this work

Reflectance confocal microscopy (RCM) enables high-resolution, non-invasive cellular imaging but suffers from motion artifacts and reliance on structural contrast alone. Dynamic analysis, leveraging subcellular motion to generate metabolic signatures, enhances diagnostic capability. Existing relevant techniques, such as laser speckle contrast imaging (LSCI) and dynamic optical coherence tomography (DμOCT), provide metabolic contrast but lack the lateral resolution and clinical adoption of RCM. Spectrally encoded confocal microscopy (SECM) offers high-speed imaging using diffraction gratings but faces challenges from swept-source laser spectral jitter, affecting image stability. This study introduces a dynamic imaging approach using stability-enhanced SECM with subpixel-level jitter correction. By integrating fiber Bragg grating (FBG) signals and jitter correction algorithm, we substantially improved image stability. Spatiotemporal Gaussian filtering and Fourier-based analysis enabled dynamic SECM (D-SECM) imaging, validated through phantom studies and ex-vivo tissue experiments. Our real-time D-SECM demonstrated enhanced metabolic contrast, paving the way for high-speed, dynamic RCM applications in biomedical imaging.

POSTER NUMBER:
10

PARISA KAVIANI, MD

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Augmentation In Ai Models: Enhancing Radiology Impressions Through Comparative Validation, Prompt-Based Learning, And Rouge Evaluation

Investigators: P. Kaviani, R. Krishna, S. Agarwal, R. Brooks, K. J. Dreyer, S. R. Digumarthy, M. K. Kalra, RSNA: Radiological Society of North America 2025

Purpose: To address the limitations of NLP and/or clinical language understanding (CLU) based generation of auto-impression from radiology findings, we explored if a prompt-based LLM (ATARI based on GPT 4o) can augment the performance of an NLP-CLU-based auto-impression generator in a multicenter, multispecialty radiology reports dataset.

Methods and Materials: Our IRB-approved study included 2,000 consecutive radiology reports belonging to adult patients, where the impression section was generated using Powerscribe Smart Impression from four radiology practices. Two physician coinvestigators classified differences between the PSI and final impressions (FI) in reports: minor differences (addition/change/deletion of single sentence/number/word/diagnosis in PSI to generate FI) and major differences (change in the entire PSI or multiple sentences, numbers, or diagnoses). Then, we applied prompt-based LLM to generate new impressions (LLM-I) for all PSI requiring changes (n=874) and reassessed LLM-I with the same classification criteria.

Results: The PSI and FI impressions were identical for 56.3% (1,126/2,000) reports. Major changes were required for 777 (38.85%) reports, with 9 (0.45%) reports needing complete revision. LLM-I “fixed” issues associated with 109/874 reports (12.47%) where PSI required minor changes and 33/874 reports (3.77%) where PSI had major changes. The results were generalizable across all four practice centers.

Conclusions: Our multicenter, real-world auto-impression clinical implementation data demonstrate that NLP-CLU and LLM can help generate an accurate impression section from the findings section with either no or minor modifications.

Clinical Relevance/Application: LLM-generated impressions can help troubleshoot performance issues related to NLP-CLU-generated impressions.

Biomedical Imaging

POSTER NUMBER:
11

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Imaging the Role of Skull Bone Marrow Immunity in Chronic Low Back Pain: A Positron Emission Tomography Study

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Using [11C]PBR28 positron emission tomography (PET), our group demonstrated elevated levels of the translocator protein (TSPO), a putative marker of immune cell density, in the bone marrow of patients with Migraine with Aura. Similar TSPO PET signal elevations were subsequently reported in neurodegenerative disorders, supporting a role for skull immune activation in various disorders linked to neuroinflammation. The aims of this study were to 1) extend these observations to another chronic pain condition, chronic low back pain (cLBP), and 2) evaluate their relationship with aging and clinical symptoms. Eighty-four patients (mean age [SD]: 47 [19]) with cLBP underwent a 90-minute integrated [11C]PBR28 PET-MR imaging. Standardized uptake value (SUV) images were computed from 60-90 min PET data and normalized to the standard structural MNI152 template. FSL-FEAT software was used to perform skull bone-focused voxel-wise multiple regression analyses to test the association between TSPO, age, and all PROMIS-29 questionnaire domains (physical function, anxiety, depression, sleep disturbance, ability to participate in social roles, pain interference, and pain intensity), correcting for genotype and, in PROMIS-29 domain analyses, age. The TSPO signal was negatively correlated with age in a widespread portion of the skull and, more focally, positively correlated with the severity of anxiety, depression, sleep disturbance, and pain interference ($p's<0.001$). These results suggest that skull bone marrow immunity may be linked to cLBP and its associated psychological and functional impairments, highlighting its potential role in pathophysiology of cLBP, and perhaps other conditions characterized by brain inflammation.

Biomedical Imaging

POSTER NUMBER:
12

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Harvard Dots (H-Dots) as a Versatile Theranostic Platform for Image-Guided Surgery and Targeted Drug Delivery

Investigators: S. M. Paranjape, S. Kashiwagi, H. S. Choi

Traditional pharmaceutical compounds often suffer from poor bioavailability, systemic toxicity, and off-target effects. To address these limitations, nanocarriers have been extensively explored for diagnosing and treating various human diseases. A key advancement in this field is the integration of diagnostic and therapeutic functionalities, known as theranostics, which enables real-time tracking of drug biodistribution and therapeutic response. However, significant challenges remain in developing platform technologies that maintain a consistent pharmacokinetic profile regardless of the payload while ensuring precise tissue targeting and minimizing nonspecific uptake.

Harvard dots (H-dots) have been developed as a promising multifunctional theranostic platform to overcome these barriers. This formulation consists of an ε-polylysine backbone with tunable charges, near-infrared fluorophores for intraoperative imaging, and β-cyclodextrins for drug encapsulation and controlled release. Clinically, H-dots have demonstrated high efficacy in fluorescence-guided surgery for tumor resections, enhancing real-time visualization of malignant tissue while reducing residual tumor burden. Furthermore, H-dot inclusion complexes with both anticancer and non-cancer small-molecule therapeutics exhibit a reproducible pharmacokinetic profile consistent with the blank carrier, rapid renal clearance independent of drug properties, and efficient drug delivery to target tissues.

To facilitate the clinical translation of H-dot technology, multidisciplinary collaborations between academic researchers, industry partners, and regulatory agencies are essential. Optimization of H-dot formulations for specific drug combinations will further refine their role in personalized medicine, offering tailored therapeutic and diagnostic solutions for oncology, inflammatory diseases, and beyond. With their unique pharmacokinetic stability and dual imaging-therapeutic capabilities, H-dots have the potential to revolutionize intraoperative precision and targeted treatment strategies.

Biomedical Imaging

POSTER NUMBER:
13

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Claudin 18.2 as a biomarker for imaging and radioligand therapy of gastric and pancreatic tumors

Investigators: S. J. Raheem, S. Bashyal, A. Haj-Merzaian, Y. Khazaei Monfared, U. Mahmood, P. Heidari, S. A. Esfahani

Gastric cancer (GCa) and pancreatic ductal adenocarcinoma (PDAC) are among the deadliest cancers worldwide. Patients with advanced GCa or PDAC typically receive chemotherapy or a combination with immunotherapy; however, survival rates remain poor. Thus, early diagnostic and therapeutic strategies are urgently needed.

Claudin 18.2 (CLDN18.2), a tight junction protein, plays a crucial role in cell integrity and homeostasis. Under normal physiological conditions, CLDN18.2 is buried between cells, and they are inaccessible. However, in cancer, particularly GCa and PDAC, CLDN18.2 is overexpressed on cell membranes, making it an accessible target. Studies show that high expression of CLDN18.2 correlates with poor prognosis and tumor progression. Due to its high expression in tumor cells, CLDN18.2 is an ideal target for both imaging and therapy (theranostic).

We aim to develop a theranostic strategy using CLDN18.2 monoclonal antibody (CLDN18.2-mAb) for molecular imaging and targeted radiopharmaceutical therapy to improve the patients outcome. Here we demonstrate the labeling of Zolbetuximab (CLDN18.2-mAb) with zirconium-89 ($[^{89}Zr]Zr^{4+}$), successfully imaging GSU, PATU8988S, and HUPT-4 tumor models of GCa and PDAC in nude mice, respectively. The uptake of radiolabeled CLDN18.2-mAb was three to four times higher in tumors compared to the nonspecific $[^{89}Zr]$ Zr-IgG-mAb tracer, as observed in positron emission tomography (PET) imaging and biodistribution studies using a gamma counter. Additionally, labeling CLDN18.2 with lutetium-177 (therapeutic radionuclide with beta emission) stopped tumor growth in GSU and PATU8988S models for nearly 4 to 8 weeks post-treatment and led to tumor shrinkage in most HUPT-4 models with better survival in comparison to control groups.

Biomedical Imaging

POSTER NUMBER:
14

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The Human Dynamic NeuroChemical Connectome (HDNCC) Scanner: A Brain-dedicated PET Scanner Integrated with the 7-T MRI Siemens Magnetom Terra

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Positron Emission Tomography (PET) is the best imaging modality for in vivo studies of neurotransmitters, receptors, and neuromodulation in humans in vivo, perfectly complementing the anatomical and hemodynamic insights from Magnetic Resonance Imaging (MRI). However, PET lacks the temporal resolution to track neurochemical dynamics on timescales comparable to cognitive processes.

We're developing the Human Dynamic NeuroChemical Connectome (HDNCC), an imaging system that integrates a novel ultra-high-sensitivity, brain-dedicated PET camera (NeuroSphere-PET) with a clinical 7T MRI scanner, allowing investigators to merge the dynamic functional capabilities of both modalities. NeuroSphere-PET's innovative spherical geometry aims to achieve tenfold higher sensitivity than current devices, providing unprecedented temporal resolution for an MR-compatible PET scanner and spatial resolution approaching state-of-the-art.

Developing this PET scanner requires detectors with exceptional performance that are also 7T MR-compatible and modular for flexible arrangement within a clinical MRI bore. Monte Carlo simulations indicate approximately 25% sensitivity across the entire brain. Preliminary PET detector characterization shows ~1.5 mm spatial resolution, less than 500 ps time-of-flight resolution, and ~5 mm depth-of-interaction resolution. With the system design finalized and manufacturing underway, we're progressing toward assembly and testing.

Initial studies will focus on characterizing resting-state changes in glucose metabolism using functional FDG-PET and their relationship to hemodynamic changes observed with BOLD-fMRI. Additionally, we'll explore dopamine receptor signaling dynamics through repeated microdose pharmacological challenges. The HDNCC scanner holds the potential to transform our understanding of neurological disorders by enabling real-time mapping of neurochemical interactions underlying cognitive processes, aligning well with the NIH BRAIN Initiative's goals.

Biomedical Imaging

POSTER NUMBER:
15

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Time of Flight Magnetic Resonance Angiography at 7T: A Comparison with 3T

Investigators: S. A. Valencia, F. Machado-Rivas, O. Afacan, C. Jaimes

Understanding cerebrovascular abnormalities in pediatric patients requires advanced imaging techniques. Time-of-flight (TOF) magnetic resonance angiography (MRA) is widely used, but higher field strengths may offer improved visualization. This study evaluates vessel contrast, vascular volume, and motion artifacts in 7T TOF MRA compared to 3T TOF MRA in pediatric patients and individuals with childhood-onset vascular conditions.

We examined seven adolescent and young adult participants, including healthy volunteers and patients with pediatric onset moyamoya disease, who underwent imaging at both 3T and 7T. TOF images were obtained at a higher spatial resolution at 7T. Vessel contrast was assessed by comparing signal intensity between arteries and adjacent brain tissue. Vascular volume was measured using specialized imaging software, and motion artifacts were graded by a neuroradiologist.

Here we show that 7T TOF MRA significantly enhances vessel contrast, particularly for smaller arteries, and increases detectable vascular volume compared to 3T. The improved spatial resolution at 7T enables better visualization of small vessel structures, which is critical for evaluating cerebrovascular diseases. Motion artifacts were slightly more pronounced at 7T, but the difference was not statistically significant, suggesting feasibility for clinical use.

These findings highlight the potential of 7T TOF MRA for assessing small vessel diseases, arteriovenous malformations, and cerebrovascular abnormalities in pediatric patients. The ability to visualize finer vascular structures could improve diagnostic accuracy and advance research in cerebrovascular imaging.

POSTER NUMBER:
16

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Dual-Channel NIR Fluorescence Imaging with Indocyanine Blue and Indocyanine Green for Enhanced Intraoperative Surgical Guidance

Investigators: A. Yamashita, P. Jang, K. Bao, S. Kashiwagi, H. S. Choi

Single-channel near-infrared (NIR) imaging at 800 nm is often insufficient for providing comprehensive diagnostic information during surgery, limiting real-time tissue differentiation and procedural guidance. In this study, we assess indocyanine blue (ICB), an analog of indocyanine green (ICG) with a shorter polymethine bridge, as a novel fluorophore for multi-channel intraoperative imaging. ICB exhibits peak absorption and emission approximately 100 nm shorter than ICG, positioning it within the 700 nm range of the NIR window. This shift allows for improved spectral separation when used alongside conventional 800 nm fluorophores, enabling dual-channel imaging.

ICB demonstrated excellent aqueous solubility, favorable optical properties, and rapid systemic clearance, likely due to its lower molecular weight. These attributes facilitate its application in critical surgical procedures, including real-time angiography, cholangiography, and sentinel lymph node mapping, with minimal background interference. Furthermore, we achieved dual-channel imaging of tumors and lymph nodes by pairing ICB with a tumor-targeting fluorophore, enhancing intraoperative visualization and precision. This capability holds significant potential for improving surgical decision-making, reducing complication rates, and optimizing patient outcomes. The incorporation of ICB into clinical imaging protocols may advance fluorescence-guided surgery by providing more accurate anatomical and functional insights, ultimately leading to improved diagnostic accuracy and therapeutic efficacy.

POSTER NUMBER:
17

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5-5-5 ABRT (Adaptive Bridging Radiation Therapy) – Artificial Intelligence Enters the CAR (-T) in Relapsed/ Refractory Large B-Cell Lymphoma

Investigators: H. S. Ababneh, A. K. Ng, J. Wan, T. Walburn, L. Zhu, M. Bobic, P. C. Johnson, J. Bredtfeld, J. Soumerai, J. S. Abramson, J. Barnes, R. Takvorian, M. J. Frigault, J. Pursley, C. G. Patel

Bridging radiation therapy (BRT) is effective for local control in patients with relapsed or refractory large B-cell lymphoma (LBCL) who are undergoing CAR T-cell therapy. We hypothesized that adaptive bridging RT (ABRT), which can be used to personalize radiation dose, fractionation, and volume based on real-time lymphoma target volume, is feasible, safe, and effective for local control.

We conducted a pilot study investigating, once weekly, CT-based adaptive RT at a dose of 5 Gy per fraction for up to 5 fractions over 5 weeks ('5-5-5') in patients referred for BRT.

Ten patients were enrolled. Eleven sites were irradiated for palliative purposes, achieving an overall symptomatic response rate of 100%. Of the 40 total ABRT sessions, 26 fractions were delivered (65%). For 8 of the 11 target volumes treated, ABRT was held after the first one or two fractions. The in-field responses during ABRT pre-CAR T were: complete response (CR) (n=3, 30%), partial response (n=6, 60%), and in-field progression (n=1, 10%). Following CAR T, the best overall response rate was 70% (n = 7), all of whom achieved CR. Among all 10 patients, 3 experienced in-field recurrence following start date of BRT. Grade 3 ICANS occurred in 3 patients. No grade 3 or higher CRS events were reported.

We demonstrate the safety and feasibility of the '5-5-5 ABRT' approach, even in patients with high-volume disease, with the vast majority responding to 1 to 2 fractions of 5 Gy. All patients achieved symptomatic relief and were able to proceed to CAR-T infusion.

Cancer

POSTER NUMBER:
18

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Photodynamic Therapy Stimulates the Immune System and Potentiates Immunotherapy in a Pancreatic Cancer Model

Investigators: D. Allen, M. Saad, T. Van Bergen, T. Hasan

Despite significant medical and scientific progress, pancreatic cancer remains highly resistant to treatment, with a generally poor prognosis. Immunotherapy, which enhances the body's immune system to fight cancer, represents a major breakthrough in cancer therapy. However, treatments like anti-PD1 therapy are effective in only a small fraction of pancreatic cancer cases. This limited efficacy is due to several factors: pancreatic cancers have few strong neoantigens to train T cells, a dense stroma that acts as a physical barrier, and a microenvironment rich in immune-suppressive cells that deactivate anti-tumor responses.

In this study, we investigated the combination of visudyne-based photodynamic therapy (PDT) with anti-PD1 treatment in a mouse model of pancreatic cancer. The results showed a significant improvement in survival, with 50% of the mice achieving complete recovery. PDT induced necrosis in tumor cells, tumor-associated macrophages, regulatory T cells, and cancer-associated fibroblasts. This process disrupted the tumor's stroma, released tumor antigens, and suppressed immune-inhibitory pathways, such as those that convert macrophages and dendritic cells into immune-suppressive states. Consequently, PDT stimulated antigen-presenting cells and caused more cytotoxic T cells to enter the tumor region, thus enhancing the effectiveness of anti-PD1 therapy.

Our findings demonstrate that PDT has an immune-stimulatory effect on pancreatic cancer, making it a promising candidate for combination therapy with immunotherapy. This approach could potentially overcome the limitations of current treatments and improve outcomes for patients with this challenging disease.

POSTER NUMBER:
19

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Heterogeneity of Circulating Tumor Cells: Understanding the Complex Biology of CTC-Immune Cell Hybrids

Investigators: D. Haber, M. Toner, D. Gulhan, S. Maheswaran

Circulating tumor cells (CTCs) are precursors of metastasis, yet only a few that enter the blood are viable and competent to form metastasis. The decrease in CTC numbers upon shedding may be due to apoptosis from anoikis, encountering an unfavorable microenvironment, or active removal by white blood cells (WBCs). While immune cells responsible for CTC destruction remain unknown, previous reports have suggested the existence of hybrid CTC/WBC cells. Using an mCherry-labeled B16F10 melanoma model in GFP-expressing mice, we identified dual-positive cells (mCherry+/GFP+) in both blood and lung tissue at protein and mRNA levels. Single-cell analysis revealed distinct characteristics based on tumor location: blood-derived dual-positive cells exhibited CTC-like copy number variations (CNV) and tumor signatures, while lung-derived populations showed diploid genomes and macrophage-specific transcriptional profiles. Further characterization of circulating dual-positive cells revealed two distinct subpopulations: one expressing platelet markers and another lacking platelet association. This heterogeneity in circulating tumor cell populations provides new insights into the complexity of metastatic progression and suggests diverse mechanisms by which tumor cells may adapt and survive during dissemination.

Cancer

POSTER NUMBER: **20**

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Modulating PARP1 activity with Stearoyl-CoA desaturase to regulate DNA damage repair in GBM

Investigators: R. Awwad, H. Mnatsakanyan, C. E. Badr

Glioblastoma (GBM) is the most common malignant brain cancer in adults, notorious for its aggressiveness and resistance to therapy. Patients with GBM are often treated with radiation therapy alongside temozolomide (TMZ) to induce DNA damage and cytotoxicity in tumor cells. However, the tumor has an ability to actively repair DNA damage, particularly in glioma stem-like cells (GSCs), rendering the current treatment ineffective and thus leading to a poor prognosis for GBM patients.

In efforts to sensitize cancer cells to radiation and TMZ, previous research from our group has explored the role of Stearoyl-CoA desaturase 1 (SCD1), specifically in mediating fatty acid desaturation and thus offering cryoprotection to GSCs. Inhibiting SCD1 has been shown to prevent tumor initiation and hinder DNA damage repair. However, the role of SCD5, an SCD isoform highly expressed in the human brain, remains unexplored.

Our findings show that downregulation of SCD1/5 in GSCs resulted in significantly decreased levels of PARP1, increased DNA damage, and reduced DNA damage repair and chromosome assembly. Conversely, cells overexpressing SCD1/5 exhibited higher PARP1 expression and lower levels of basal DNA damage compared to control GSCs.

Under normal conditions, PARP1 scans for base excision and other forms of DNA damage. When SCD is inhibited, fatty acid desaturation is reduced, leading to an accumulation of DNA damage and over-activation of PARP1. In conclusion, our findings provide a direct link between fatty acid metabolism and PARP1-mediated DNA damage repair, highlighting the importance of advancing our understanding of SCD1 and SCD5's roles in GBM.

POSTER NUMBER: **21**

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Pooled transcription factor overexpression screening uncovers novel regulators of chemoresistance in pancreatic ductal adenocarcinoma

Investigators: J. W. Bae, D. H. Gong, W. L. Hwang

Pancreatic ductal adenocarcinoma (PDAC), the most common type of pancreatic cancer, is an aggressive and lethal disease that is highly refractory to standard-of-care chemotherapy. Therapeutic approaches include the use of cytotoxic agents like gemcitabine and novel KRAS inhibitors (KRASi) are also emerging as promising treatment modalities. Resistance to therapy is mediated by both cell-intrinsic and extrinsic properties, which are in large part driven by transcription factors (TFs). In PDAC, for instance, certain cancer cell states like the basal subtype is driven by a master TF, deltaNp63, and is characterized by an increase in cell motility and mesenchymal features that enhance tumor growth and invasion. Despite our current knowledge of the relationship between TFs and malignant cell states in PDAC, we do not yet have a comprehensive understanding of the diverse landscape of TF-driven transcriptional networks and associated cellular phenotypes that collectively drive therapeutic resistance. To investigate this question, we employed a high-throughput barcoded open-reading frame (ORF)-based pooled screen to systematically perturb and dissect the role of all known human TF isoforms mediating chemoresistance in refractory PDAC. We uncovered novel TFs like nuclear factor I/B (NFIB) that confer resistance to both cytotoxic (gemcitabine) and oncogene-targeted (KRASi) therapy and genetically engineer isogenic model systems for deeper characterization of cell-intrinsic and extrinsic phenotypes. We anticipate that this work will significantly advance our understanding of treatment resistance in PDAC and lead to potential avenues for combination therapy in the future.

POSTER NUMBER:
22

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Pilot Feasibility Trial of a Supportive Care Digital Application for Patients with Advanced Non-Small Cell Lung Cancer

Investigators: M. C. Boulanger, S. B. Lo, J. A. Centracchio, B. Jewett, M. Freese, M. Holtze, J. M. Jacobs, L. A. Petrillo, J. Bauman, A. El-Jawahri, J. S. Temel, J. A. Greer

Background: Patients with advanced non-small cell lung cancer (NSCLC) experience burdensome symptoms, psychological distress, and poor quality of life. We developed and pilot tested a digital health application ("THRIVE"), consisting of 6 modules designed to improve patients' symptom management and coping with NSCLC.

Methods: Eligible patients included adults within 12 weeks of an advanced NSCLC diagnosis receiving care at two academic medical centers and four community affiliates. Participants were randomized to THRIVE and usual care or usual care alone. Participants completed baseline and 12-week assessments of quality of life (Functional Assessment of Cancer Therapy-Lung), physical symptoms (MD Anderson Symptom Inventory; MDASI), psychological distress (Hospital Anxiety & Depression Scale), and coping (Brief COPE). The primary outcome was study feasibility, defined as ≥65% of approached patients consenting to participate; ≥70% of intervention participants completing ≥4 of 6 app modules; and ≥70% of the sample completing the 12-week assessments. We used the System Usability Scale to assess intervention acceptability.

Results: Of 232 patients approached, 135 (58.2%) provided consent, and 120 (51.7%) were randomized (Agemean=67.90 years, 61.7% female, 90.8% white). Among intervention participants, 70.5% (43/61) completed ≥4 modules, with 77.3% reporting above-average System Usability Scale ratings for THRIVE. Ninety-four (78.3%) participants completed the 12-week assessments.

Conclusions: Although the enrollment rate was lower than anticipated, patients with advanced NSCLC who received THRIVE met the feasibility criterion for app completion and reported high acceptability. These results support conducting a follow-up efficacy trial of THRIVE for improving patients' quality of life, physical symptoms, and other psychosocial outcomes.

Cancer

POSTER NUMBER:
23

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Engineering and Stimulation of Dendritic Cells for Cancer Immunotherapy

Investigators: R. Das, E. A. Halabi, I. R. Fredrich, X. Ge, J. Oh, H. M. Peterson, E. Scott, R. H. Kohler, F. Fei, S. Parvanian, C. S. Garris, R. Weissleder

Dendritic cells (DCs) represent a critical bridge between innate and adaptive immunity and are major antigen-presenting cells controlling T-cell responses. The efficient activation of DCs in tumors and lymph nodes is essential to the design of next-generation cancer vaccines. The challenge is to stimulate DCs without causing excessive toxicity. We hypothesized that a multi-pronged combinatorial approach to DC stimulation would allow dose reductions of innate immune receptor-stimulating agonists while enhancing drug efficacy. We developed a hybrid lipid nanoparticle (LNP) platform that primes DCs via two distinct cellular pathways: Toll-Like Receptor3 (TLR3) pathway using poly I:C and non-canonical NFkB pathway (NIK) through LCL-161 utilizing a smaller, cross-linked cyclodextrin nanoparticle (CDNPs) as a "sponge," thus featuring a "Nanoparticle-in-a-Nanoparticle" design. We observed a high level of IL-12, mostly in cells with DC morphology, and a significant reduction in tumor cells in the treated mice. A single administration of these hybrid LNPs using doses of only 5 μg poly I:C completely eradicated tumors in the murine MC38 model. In a subsequent study, DCs were engineered by LNP-mRNAOVA ex vivo to sidestep the systemic toxicity of LNPs, and the mice vaccinated with the engineered DCs generated a strong CD8 T-cell response. When challenged with B16-OVA, tumor volume increased in the control group at a ≈10 times higher rate than the engineered DC vaccinated group, translating into substantially enhanced survival. Our studies show the therapeutic potential of both in situ immune stimulation by dual pathways and ex vivo engineering of DCs as promising cancer vaccine platforms.

POSTER NUMBER:
24

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Targeted Therapy with CDK4/6 Inhibitors in IDH-Mutant Gliomas

Investigators: J. Miller, D. Cahill, H. Wakimoto

IDH-mutant gliomas often recur despite standard treatments, such as radiation and chemotherapy, driven by genetic alterations and treatment resistance, which contribute to their aggressive progression. Over 20% of recurrent IDH-mutant gliomas exhibit homozygous loss of CDKN2A, leading to the loss of p16, an endogenous CDK4/6 inhibitor, and aberrant signaling through the CDK-Rb pathway. We hypothesized that CDKN2A loss drives CDK4/6 inhibitor sensitivity in these tumors. Given the frequent co-occurrence of CDKN2A loss, CDK4/6 inhibition may offer a promising therapeutic strategy. Since CDK inhibitors are already approved for other cancers, they hold the potential for treating IDH-mutant gliomas. We assessed the sensitivity of patient-derived IDH-mutant glioma cell lines (astrocytoma, oligodendroglioma) with and without CDKN2A homozygous deletion to CDK4/6 inhibitors. CDKN2A-deleted gliomas showed increased sensitivity to CDK inhibition compared to non-deleted cell lines, confirming CDK4/6 dependency in this subset. Among the inhibitors, Abemaciclib demonstrated the strongest effect, followed by others. Given the challenge of resistance to CDK4/6 inhibition, we are exploring combination therapies targeting complementary pathways. Further investigation will include testing additional CDK4/6 inhibitors and exploring combinations with other targeted treatments to overcome resistance. Preclinical resistance models and clinical trials will help optimize therapeutic strategies while identifying biomarkers of response could aid in personalizing treatment approaches.

Cancer

POSTER NUMBER:
25

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A Novel Self-Assembling Vaccine, VTX-067, targeting E6/E7 proteins of Human Papilloma Virus Induces T Cell-Mediated Immune Responses and Inhibits Tumor Growth in a Murine Model of Cervical Cancer

Investigators: Y. Gemechu, S. Mukherji, J. A. Gelfand, T. Brauns, A. E. Sluder, P. R. Leblanc, G. Steinfels, P. Korner, I. Capila, Z. Shriver, P. M. Reeves, M. C. Poznansky

An increasing subset of squamous cell cancers including cervical, head and neck cancer, anal and penile cancers are caused by Human Papillomavirus (HPV). The available prophylactic HPV vaccines are effective in preventing HPV infection but are less relevant in treating an already established tumor. To fill this significant unmet need for new broadly applicable therapeutic vaccines for HPV induced cancer, we developed a novel broadly applicable and modular immune activating self-assembling vaccine (SAV) which consists of a modified Mycobacterium tuberculosis heat shock protein70 (MTbHsp-70) fused with avidin (MAV) as an adjuvant that simply self assembles with biotinylated immunogenic peptides targeting the E6 and E7 proteins of HPV (VTX-067). VTX-067 elicited robust antigen specific CD4+ and CD8+ T cell responses and protected mice in a subcutaneously generated TC-1 tumor model as monotherapy or with anti-mPD1. Three dose levels of VTX-067 provided both significant T cell mediated viral antigen specific responses, increases in overall survival and reduction of tumor volume at two different anatomical sites. We demonstrate a combinatorial benefit of immunomodulatory drug, Lenalidomide, with suboptimal doses of VTX-067, in inhibiting TC-1 tumor growth along with a significant improvement in overall survival. By employing CD4+ and CD8+ T cell depletion and adoptive T cell transfer experiments, we demonstrate the critical roles of vaccine primed CD8+ T cells for VTX-067 efficacy. Overall, our study demonstrated that VTX-067 was safe and well-tolerated in mice. Taken together, these data support the further development this of self-assembling vaccine platform for clinical use.

POSTER NUMBER:
26

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Targeting the stem-like cell state in IDH-mutant gliomas with chimeric antigen receptor (CAR)-T cells

Investigators: D. Gerovasilis, S. Dumont, C. Mount, S. K. Kovatsis, J. Lu, J. Zhong, E. Boxer, D. Cahill, I. Tirosh, M. Suva

Isocitrate dehydrogenase (IDH)-mutant glioma is the most common primary glioma in adults under 50 years old. Despite recent advances in targeted therapies for patients diagnosed with low-grade IDH-mutant gliomas, patients with more aggressive disease still face limited treatment options. While there have been prior efforts to use the immune system to target IDH-mutant gliomas, these therapies have yet to be proven clinically effective. One hypothesis is heterogeneous tumor populations limit the effectiveness of these therapies. Prior work in our laboratories using single cell RNA sequencing (scRNAseq) in IDH-mutant gliomas has identified a stem-like cell population as the primary cellular component driving disease progression. Chimeric antigen receptor (CAR)-T cell therapies may offer the potential for targeting this stem-like cell state. Thus, we hypothesize that a stem-like state-targeting CAR-T cell could offer a new therapeutic strategy in IDH-mutant gliomas. We report screening of a panel of CAR-T cells designed against potential targets identified from scRNAseq data. We identify several candidate targets which are highly expressed in the stem-like state and the development of CAR-T cells with activity in in vitro IDH-mutant cell line assays. Additionally, we show evidence of activity against patient-derived IDH-mutant organoid models. Finally, we demonstrate the function of these CARs against in vivo xenograft models in immunocompromised mice. Using transcriptional and protein-level readouts, we assessed the effectiveness of stem-like state targeting in both in vitro and in vivo models. Taken together, our findings support the use of scRNAseq data to design targeting strategies for CAR-T cells in IDH-mutant gliomas.

Cancer

POSTER NUMBER: **27**

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Dissecting the metabolic heterogeneity of cell states in glioblastoma

Investigators: A. Jucht, L. Bar Peled, I. Tirosh, M. Suva

Glioblastoma (GBM) is the most common and aggressive primary malignant tumor of the central nervous system and is a notoriously heterogenous disease. Recent single cell RNA-sequencing (scRNA-seq) studies have shown GBM to be comprised of various cellular states that have distinct genetic drivers and receive input from the tumor micro-environment (TME). These states have been shown to organize spatially within the tumors around areas of necrosis with the mesenchymal-like cells (MES) enriched in the tumor core whereas the more stem-like populations (NPC- and OPC-like) invade into the healthy brain. Due to this geographical distribution of states around hypoxia, we hypothesize that the metabolism of the cells play a role in determining their transcriptional profile. Here we leverage the metabolic reporter Sonar to label the NAD+ and NADH pool in our gliomasphere models and show by RNAseq that NADH/NAD+ high cells enrich for the MES-like state, whereas the NADH/NAD+ low cells are enriched for the NPC- and OPC-like states, confirming a metabolic bias in the transcriptional states. By performing spatial transcriptomics and spatial metabolomics on sister slides of patient samples, we confirm that the MES-like cells exhibit a higher glycolysis signature, while the stem-like states depend on OXPHOS for their energetic needs. By treating our glioma models with various drugs, we show that targeting the mitochondria depletes the stem-like compartment, while inhibiting glycolysis directly targets the MES-like cells. Together, this provides a better understanding of cell state biology in GBM and opens the door to rational therapeutic combinations.

POSTER NUMBER: **28**

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A ribonucleotide carbohydrate system (iRNC) enhances antigen presentation and controls glioblastoma

Investigators: H. Kim, J. Oh, J. Jeon, F. Fei, C. Garris

Lipid nanoparticle (LNP)-formulated messenger RNA (mRNA) vaccines are emerging as a major platform for the rapid development of disease- and patient-specific vaccines. To orchestrate a more robust adaptive immune response while minimizing off-target effects, thousands of lipids and nucleoside modifications have been investigated. Systemic vaccination can generate more robust T cell responses, but clinical challenges, particularly with systemic administration, have been a hurdle in vaccine development. Here we show an alternative strategy for more efficient systemic mRNA delivery to enhance antigen presentation. We developed synthetic immuno ribonucleocarbohydrate (iRNC) complexes based on fluorinated cyclodextrin nanoparticles capable of encapsulating mRNA payloads and containing flexible small molecule drug payloads for NFkB stimulation as adjuvants. iRNC were more efficient and less toxic compared to LNP and lipofectamine mRNA delivery vehicles. Utilizing ovalbumin (OVA) as a model antigen, we demonstrate significantly enhanced innate immunity in a glioblastoma mouse model with excellent tolerability. The strategy of enhanced transfection efficiency of tumor mRNA coupled with dendritic cell targeting and stimulation is simple, modular, and possesses translational potential.

Cancer

POSTER NUMBER:
29

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Targeting Cell States in Glioblastoma Organoid Models with Chimeric Antigen Receptor-T Cells

Investigators: S. K. Kovatsis, C. Mount, E. Boxer, J. Zhong, S. Dumont, D. Gerovasilis, J. Q. Lu, I. Tirosh, M. L. Suva

Despite decades of concerted research and clinical efforts, patient outcomes in glioblastoma (GBM) remain dismal. While chimeric antigen receptor (CAR)- T cell therapies in GBM have produced isolated reports of efficacy at the individual level, these therapies have not been effective enough for widespread clinical use. It is thought that inter- and intra-patient tumor heterogeneity contributes to variable response to these therapies in clinical trials. Single cell RNA sequencing (scRNA seq) performed in our laboratories has demonstrated that this transcriptional heterogeneity can be organized along axes representing cellular states. Current CAR-T cell therapies have yet to demonstrate clear targeting of these identified cell states and their dynamic role within GBM. Based on these data, we set out to engineer CAR-T cells that will target a specific cell state. We hypothesize that CAR-T cells targeting a specific GBM cell state will lead to a depletion of those populations. We developed a screening strategy to generate candidate CAR-T cells for this application. We confirmed specific activity in vitro. As a model system, we developed patient-derived GBM organoids that recapitulate the cell state landscape seen in primary tumors. We treated GBM organoids with this CAR-T cell panel and assessed cell states by scRNA seq. Each cell state targeting CAR-T cell contributed to a global cell state shift in the surviving GBM organoid cells. We anticipate that our findings will inform foundational biology necessary for rational design of multi-target constructs for therapeutic application.

POSTER NUMBER:
30

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Analysis of treatment-associated effects in matched pre- and post-treatment pancreatic ductal adenocarcinoma using whole transcriptome spatial molecular imaging

Investigators: N. A. Lester, B. Awasthi, D. Gong, J. W. Bae, X. Yin, A. Heck, E. Stirling, M. Walter, M. Vandenberg, M. Hoang, P. Divakar, J. Beechem, D. Ting, W. L. Hwang

Pancreatic ductal adenocarcinoma (PDAC) is an aggressive and lethal treatment-refractory malignancy, in large part due to its complex cellular composition. While the molecular heterogeneity of PDAC has been well characterized through dissociated single-cell approaches, the spatial landscape remains poorly understood, particularly in patient specimens. Although spatial profiling techniques have advanced in situ annotation and mapping of cell types in PDAC, imaging at subcellular resolution has been limited to relatively small panel sizes due to limitations in resolution and increased data sparsity as panel sizes increase. The recent development of a whole-transcriptome (WTx; 18,985 targets) panel for spatial molecular imaging (SMI) offers unprecedented molecular plex at subcellular resolution which allows for unbiased discovery and spatial annotation of novel gene programs that are likely to be missed with smaller panels. We conducted SMI on matched pre-treatment biopsies and post-treatment resection PDAC specimens at subcellular resolution at both 1000-plex and whole transcriptome levels. Using the WTx panel, we identified a mean of >1000 unique genes per cell, and up to 1,700 transcripts, with up to 125,000 cells analyzed per matched pair. When used in parallel with corresponding hematoxylin and eosin-stained sections, annotated by a board-certified pathologist, our SMI data offered insights into the cellular composition and interactions of pre- and post-treatment samples. These annotations and transcriptional signatures could identify treatment-induced changes in cancer subtype and intercellular interactions. This study highlights the potential to identify novel treatment-associated effects using whole-transcriptome spatial data at subcellular resolution and thus identify potential targetable molecular vulnerabilities in PDAC.

Cancer

POSTER NUMBER:
31

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Proton Beam Therapy for Advanced Periocular Skin Cancer: An Eye-Sparing Approach

Investigators: Y. Zhang, I. C. Lima , A. A. Woo, S. Zieminski , J. A. Adams , M. A. Hughes , A. W. Chan

Background/Objectives: The management of periocular skin malignancies presents a unique challenge. Proton beam therapy, due to its sharp dose fall-off, allows for the delivery of a tumoricidal dose to the tumor while sparing adjacent normal tissues.

Methods: Thirteen patients with a median age of 76.5 years received protons at our institution to a median dose of 66.6 Gy (RBE). Sixty-four percent of the lesions were basal cell carcinoma, and 22% were squamous cell carcinoma. Eighty-six percent of patients underwent biopsy only or partial resection. Fifty-seven percent of the lesions were located in the medial or lateral canthus. There was orbital invasion in 93% of the cases. Locoregional control probability and overall survival were estimated with the Kaplan–Meier method. Treatment toxicity was scored using the CTCAE 4.0.

Results: At a median follow-up of 96 months, there was no local recurrence. The rate of orbital preservation was 100%. Functional vision was maintained in all the patients. There was no acute or late grade 3 or higher toxicity.

Conclusions: Protons allow for long-term tumor control with eye preservation in patients with locally advanced periocular skin cancers. Larger prospective multi-institutional trials with standardized ophthalmological assessments are needed to confirm our findings.

POSTER NUMBER:
32

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Evaluating a Highly Multiplexed Spatial Proteomics Platform to Study Tumor Immune Interactions in Glioblastoma

Investigators: J. Q. Lu, C. Mount, D. Gerovasilis, S. K. Kovatsis, J. Zhong, A. Greenwald, Z. Wen, I. Tirosh, M. Suvà

Understanding the spatial relationships of the tumor immune microenvironment (TIME) is paramount in deciphering the mechanisms that drive immune evasion and therapeutic resistance in solid tumors. Although single-cell transcriptomic analyses have provided invaluable insights into this heterogeneity, because they require dissociation of tissues, information about spatial relationships is lost. Recent advances in multiplexed imaging and spatial proteomics now allow us to interrogate this complexity while preserving spatial relationships. These relationships include immune infiltration, activation states, and suppressive niches within intact tissue. Understanding these features in glioblastoma (GBM) may uncover the reasons for resistance that patients exhibit to immune-targeted therapies. We hypothesize that a highly multiplexed spatial proteomics panel will uncover mechanisms of resistance to immune therapies in GBM. Here, we evaluate the potential of the Akoya Phenocycler platform as a highly multiplexed spatial proteomic system in GBM. We introduce the development of a targeted antibody panel revealing the spatial relationships of diverse immune cell populations and heterogeneous GBM populations in primary patient tumors. We uncover cellular neighborhoods and unique spatial relationships in different histological contexts within these tumors. We demonstrate that this technology will become a valuable platform for uncovering tumor-immune interactions for patients with GBM.

Cancer

POSTER NUMBER:
33

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Transcription factor TP63 is involved in metabolic programming in esophageal cancer

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Esophageal adenocarcinoma (EAC) and squamous cell carcinoma (ESCC) are two subtypes of esophageal cancer that display different differentiation markers, and responses to treatment regimens, including chemotherapy, chemoradiation, and immunotherapy. TP63, a transcription factor involved in squamous differentiation is expressed in ESCC and notably absent in EAC. Given its similarity to p53, a known tumor suppressor and regulator of cell metabolism, we sought to determine whether p63 expression may be responsible for the distinct metabolic program in ESCC relative to EAC and whether it can be targeted.

Here we show that ESCC cells exhibited higher glycolytic metabolism phenotype with higher glucose uptake and reduced viability in response to glucose starvation, compared to EAC cells. Along with this, ESCC cells also demonstrated lower mitochondrial respiration, ATP production, and metabolic adaptability (i.e. spare capacity). Knockdown of p63 in ESCC cells resulted in an increase in mitochondrial respiration, ATP levels, as well as increased viability under glucose deprivation. Loss of p63 was accompanied by the reduction in squamous differentiation markers and an increase in glandular differentiation marker expression. Furthermore, knockdown of p63, increased glucose cycling through the tricarboxylic acid (TCA) cycle and towards fatty acid synthesis, with enhanced enzyme activity for both pathways.

Our data suggest that ESCC and EAC represent different metabolic programs. ESCC cells are more dependent on glycolytic metabolism whereas EAC exhibiting greater mitochondrial respiration. These differences are driven by the transcription factor p63 Therefore, differential metabolic targeting, for both ESCC and EAC may be a more effective treatment strategy.

POSTER NUMBER:
34

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Synergistic Effect of Minocycline and Photodynamic Priming in the Treatment of Pancreatic Ductal Adenocarcinoma

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Pancreatic ductal adenocarcinoma (PDAC) is a highly aggressive cancer, responsible for over 90% of all pancreatic cancer cases, and is currently the third leading cause of cancer-related deaths in the United States. The poor prognosis of PDAC is due to the challenges of early detection and the prevalence of advanced disease. Photodynamic therapy (PDT) offers a treatment option that utilizes a photosensitizer and light to kill cancerous cells. Additionally, photodynamic priming (PDP) leverages the subtherapeutic effects of PDT to prime remaining tumor cells, enhancing tumor chemosensitivity by altering the tumor microenvironment, vascularity, and stroma. PDT using photoactivable multi-inhibitor liposomes enables more controlled and targeted drug release by encapsulating the photosensitizer benzoporphyrin derivative and the chemotherapy agent irinotecan. Irinotecan induces DNA damage by intercalating between base pairs, but its effectiveness is limited by Tyrosyl-DNA phosphodiesterase 1 (Tdp1), which repairs the damage. Minocycline, a drug that inhibits Tdp1, can increase the efficacy of irinotecan by preventing DNA repair. In this study, we aimed to overcome chemoresistance in vivo using mouse models with PDAC through the development of mechanism-based combination therapies using three different FDA-approved drugs. Our results showed a significant increase in irinotecan uptake, and a reduction in tumor size when mice were treated with minocycline prior to a single PDT administration. Additionally, our treatment enhanced the levels of cytotoxic CD8+ T cells in the tumor while decreasing immunosuppressive regulatory T cells. This combination of may offer a promising strategy to enhance the effectiveness of both PDT and chemotherapy in treating PDAC.

POSTER NUMBER:
35

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Intraductal Papillary Mucinous Neoplasm Cellular Plasticity linked with Repeat Element Dysregulation

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Background and Aims: Intraductal papillary mucinous neoplasms (IPMNs) are preneoplastic pancreatic lesions that present on a spectrum of histologic phenotypes with variable risk in progressing to invasive cancer. Aberrant repetitive element expression has been shown to be functionally linked to cell state changes in pancreatic cancer. This study utilized spatial transcriptomics with customized repeat element probes to better understand the relationship of histologic subtypes, repeat element dysregulation, and molecular profiles of different cell populations in IPMN.

Methods: A total of 63 lesions from 22 patients with resected IPMNs of different histologies and degrees of dysplasia were analyzed with whole transcriptome spatial analysis (GeoMx). Of these, 49 lesions from 18 patients were also processed for single-cell spatial molecular imaging (CosMx). Repeat element probes for LINE1, HSATII, HERVK, and HERVH were used for GeoMx and CosMx.

Results: Pancreaticobiliary IPMN was enriched for basal-like epithelium and infiltration of Treg cells. Intestinal IPMN was enriched for classical epithelium and macrophage infiltrates. Gastric IPMN was found to have equal basal-like and classical epithelium with a diverse immune infiltrate. Repeat RNAs were expressed at high levels across IPMN phenotypes and enriched in high-grade dysplasia. Single-cell transcriptional trajectory analysis reveals a phylogeny starting from Gastric IPMN to Intestinal and Pancreaticobiliary branches associated with higher-grade dysplasia and repeat RNA expression.

Conclusion: Spatial transcriptomics of IPMN identified transcriptional plasticity between gastric, pancreaticobiliary, and intestinal histologies and a molecular continuum between these cell states. Elevated repeat element expression was linked with cells in transition between cell states and identified progression.

Cancer

POSTER NUMBER:
36

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Tailored Hybrid Biomimetic Nanovaccine (HBNV) for KitK641E-Mutant Melanoma: Fabrication, Functional Validation, and Immunotherapy Reinvigoration

Investigators: K. Poudel, Z. Ji, C. N. Njauw, A. Rajadurai, B. Bhayana, R. J. Sullivan, J. O. Kim, H. Tsao

Cancer nanovaccines provide a promising avenue for personalized and precision immunotherapy by enabling robust immune stimulation. Effective antitumor responses require coordinated interactions between antigen-presenting cells (APCs), tumor cells, and immune effectors. Leveraging nanomedicine, we developed a hybrid biomimetic nanovaccine (HBNV) that integrates tumor and APC membrane proteins as antigens and targeting ligands, along with an immunoadjuvant to enhance immune activation. Given the resistance of KIT-mutated acral and mucosal melanomas to standard therapies, our study shows that HBNVs efficiently internalized into target cells, promoted APC maturation, stimulated antitumor cytokine release, facilitated cytotoxic T cell infiltration into the tumor microenvironment (TME), suppressed immunosuppressive signals and exhibited homotypic effects within the TME and lymphoid organs. These effects resulted in a 76.0% tumor volume reduction ($p = 4.95E-16$) in therapeutic models and a significant reduction in prophylactic tumor burden (HBNV mean TV = 274.8 mm^3 vs. control mean TV = 992.3 mm^3, $p = 2.43E-08$). Gene ontology analysis identified immune stimulation as the top biological process upregulated in HBNV-treated tumors. Bulk RNA sequencing deconvolution revealed increased B cell and CD8+ T cell populations, with significant enhancements in immune infiltration ($p < 0.000001$) and tumor microenvironment remodeling ($p < 0.000001$). Additionally, tertiary lymphoid structures (TLS) analysis showed elevated gene expression across renal ($p < 0.0001$), gastric ($p < 0.0001$), and melanoma ($p = 0.0028$) TLS signatures. Our findings underscore the transformative potential of HBNVs in overcoming immunotherapeutic resistance, offering a personalized and adaptive strategy to enhance innate and adaptive antitumor immunity in mutant melanoma.

POSTER NUMBER:
37

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Proton Flash-Arc Therapy (PFAT): A Novel Approach for Cancer Radiotherapy

Investigators: B. Rothwell, A. Bertolet, J. Schuemann

Radiotherapy is an effective cancer treatment, aiming to maximize tumor eradication while minimizing healthy tissue damage. Our research introduces a novel approach that integrates proton, arc, and flash radiotherapy to enhance treatment effectiveness.

Proton therapy can offer superior precision compared to X-rays, with the Bragg peak delivering a high dose at the tumor site and reducing healthy tissue exposure. However, it is sensitive to uncertainties in tumor location and can produce linear energy transfer (LET) hotspots beyond the tumor, potentially damaging nearby organs. Arc therapy mitigates this by delivering protons in an arc, smoothing out range uncertainties and LET hotspots. Flash radiotherapy, which delivers radiation at ultra-high dose rates (<1 s), has shown sparing of healthy tissue while preserving tumor control. However, maintaining these high dose rates in clinical settings is challenging.

We propose a novel technique to address these challenges: proton flash-arc therapy (PFAT). PFAT combines the precision of proton and arc therapy with flash delivery by spatially fractionating dose to healthy tissue for high dose rates, while maintaining slower delivery to the tumor to avoid sparing effects. Optimizing dose and LET distribution shifts hotspots into the tumor, enhancing biological effect. We developed an optimization framework for PFAT within OpenTPS. Our results from phantom and clinical cases show PFAT improves dose distribution, shifts LET hotspots to the tumor and achieves flash dose rates in critical regions like the brainstem, offering great promise for cancer treatment.

Ongoing work is refining PFAT for larger, more complex tumors and ensuring clinical feasibility.

Cancer

POSTER NUMBER:
38

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Interventions to Manage Fear of Cancer Progression for Patients with Advanced Cancer: A Systematic Review.

Investigators: R. Sarathy, L. A. Petrillo, M. Hernand, M. Lydston, J. Carkin, J. Temel, J. Greer, E. R. Park, D. L. Hall

Background/Purpose: For cancer survivors living with advanced cancer, fear of cancer progression (FOP) is common, characterized by hypervigilance and persistent worry. FOP is similar to fear of cancer recurrence (FCR) among patients with early-stage cancer, although it is unclear whether FCR interventions benefit advanced cancer survivors. This systematic review aimed to identify and describe randomized controlled trials (RCTs) evaluating interventions to manage FCR, FOP, or uncertainty in advanced cancer.

Methods: This systematic review followed PRISMA guidelines. A medical librarian searched Ovid MEDLINE, Embase.com, Web of Science, APA PsycInfo, and Cochrane for relevant peer-reviewed articles. Inclusion criteria were: RCTs, samples including patients with advanced cancer (stage III-IV), and interventions and outcome measures addressing FOP, FCR, or uncertainty. Studies without English translations were excluded.

Results: Of 1,546 publications identified, 20 studies met inclusion criteria. Two RCTs included patients with advanced cancer only; 18 RCTs included mixed populations of advanced and early-stage cancer. Four of the mixed-sample RCTs included a subgroup analysis of patients with advanced cancer. Eleven RCTs focused on breast or gynecologic cancers. Among RCTs that included only patients with advanced cancer, the intervention approaches included cognitive-behavioral stress management and dignity therapy; only one was adequately powered to evaluate efficacy.

Conclusions and Implications: Few studies focused on FCR/FOP among patients with advanced cancer. While several FCR studies included these patients, most lacked subgroup analyses and adequate power to determine the interventions' efficacy in this population. Given increasing numbers of advanced cancer survivors, targeted interventions addressing FOP are needed.

POSTER NUMBER:
39

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Deep Profiling of Immune Reconstitution Following Radiation Treatment for Oligometastatic Prostate Cancer Identifies Immune Signatures Associated with Recurrence

Investigators: J. J. Smith, R. Dzeng, Y. Otani, D. Qi, I. Pompa, R. Pittie, E. Chung, K. Otani, J. Wo, A. Zietman, E. Van Allen, J. A. Efstathiou, D. T. Miyamoto, P. M. Reeves, S. C. Kamran

Background: Radiation therapy (RT) can improve survival for patients with oligometastatic prostate cancer (OMPC), though predicting long-term outcomes remains challenging. Beyond direct cytotoxicity, we hypothesize that immune reconstitution dynamics following RT-induced lymphopenia may influence durable tumor control.

Methods: We performed longitudinal immune profiling in 14 OMPC patients treated with RT. Peripheral blood mononuclear cells collected pre-RT, post-RT, and 3/6 months were analyzed via CyTOF and bulk TCR-sequencing. Analyses were performed with OMIQ, ImmunoSEQ, and scikit-learn.

Results: Among 14 OMPC patients that received RT (median age 62.5 years), 8 experienced tumor recurrence (defined as PSA recurrence, median time-to-recurrence: 26 months). RT induced significant lymphopenia ($p = 0.0008$), with a significantly lower nadir in non-recurrent patients ($p = 0.0022$). CyTOF identified 18 significantly altered immune subsets, logistic regression linked CD4+/CD8+ EMRAs, plasmacytoid DCs and NK-cell to recurrence, while NKT-cells, Treg-like cells, and B-cells were associated with non-recurrence. TCR sequencing revealed that increased repertoire diversity post-RT is associated with non-recurrence (Morisita's index, $p = 0.0225$). Integrated analysis of CyTOF and TCR-sequencing identified that $CD8^+$ EMRA T-cells correlated with lower TCR diversity, whereas B-cells were linked to increased diversity.

Conclusions: As a first step towards identifying clinically translatable indicators of response following RT, we identified post-RT changes in specific immune populations (T-cell and B-cell subsets) and TCR-repertoire diversity that distinguish recurrence risk. These findings suggest that immune reconstitution dynamics post-RT are an important indicator of outcome. Future studies with an expanded cohort (n=66) will integrate proteomic and transcriptomic analysis to further characterize immune reconstitution post-RT.

Cancer

POSTER NUMBER:
40

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In-Vitro Modeling of Cellular Response to Radiation in Radiopharmaceutical Therapy Experiments

Investigators: V. V. Onecha, A. Bertolet

Radiopharmaceutical therapies (RPT) deliver compounds containing radioisotopes that bind with high affinity to tumor cells to irradiate them. It is known that cellular response to radiation is strongly correlated with the absorbed dose, but it is only well characterized for external beam radiotherapy, where cells receive a homogeneous and instantaneous dose. However, none of these conditions are met when cells are exposed to RPT agents, as the dose is distributed heterogeneously in both time and space. This work presents a mathematical model for cell response in 2D cell colonies to RPT agents, based on spatiotemporally heterogeneous dosimetry calculated with the TOPAS Monte Carlo toolkit.

The model considers four states for a given cell: healthy, quiescent, senescent, and apoptotic. Transitions across these states were defined with rules dependent on the instantaneous and accumulated dose per cell. The framework is discretized in time, and for each time step and cell, TOPAS calculates the absorbed dose, and the model updates the probability for a cell of being at a given state according to the transition rules and the calculated dose.

To test the model, we used data from viability assays of two cell lines treated with [211At]PTT, a targeted alpha-therapy agent that binds to PARP1 in nuclei. We optimized the transition rules by which the model best estimates the experimental data and analyzed them to approximate some radiobiological properties.

This work presents the first version of a computational model designed to investigate and analyze cell response to spatiotemporal dosimetry heterogeneities in RPT in-vitro experiments.

POSTER NUMBER:
41

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Changes in one-carbon metabolism mediate late recurrence in hormone receptor-positive breast cancer

Investigators: I. Vianna, B. Ordway, J. Kreuzer, W. Haas, D. Sgroi, L. Ellisen

While the ratio of mRNA expression of HOXB13 to IL17BR has been used as a clinical marker for late recurrence in hormone receptor-positive (HR+) breast cancer, little is known about the underlying biological mechanisms behind late recurrence. Previous studies have demonstrated that epithelial-mesenchymal plasticity can mediate the late recurrence phenotype. Proteomics analysis of 86 HR+ breast tumors revealed choline dehydrogenase (CHDH) as the most significantly upregulated protein in HOXB13 low tumors. Additionally, analysis of metabolomics data from the Broad Institute Cancer Dependency Map Portal identified 1-methylnicotinamide, a product of nicotinamide N-methyltransferase (NNMT), as the metabolite most upregulated in HOXB13/IL17BR high cell lines. CHDH and NNMT have opposing roles in regulating S-adenosylmethionine (SAM). To test the association between SAM flux and differing epithelial and mesenchymal phenotypes, we created a CHDH:NNMT score and correlated this against epithelial-mesenchymal phenotypes in patient tumors from the TCGA Firehose Legacy dataset, finding a significant association in all tumor types. In cell lines, we not only demonstrated that knockout of NNMT is sufficient to increase the expression of epithelial proteins in cell lines displaying a mesenchymal phenotype but also that CHDH overexpression can replicate this phenotype, reducing the expression of NNMT as well as multiple known mesenchymal markers. Collectively, our results indicate that the HOXB13/IL17BR ratio is linked to dysregulation of the SAM cycle, leading to changes in epithelial-mesenchymal plasticity that contribute to late recurrence.

Cancer

POSTER NUMBER:
42

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Photodynamic Therapy-Induced Immunogenic Cell Death in a 3D Heterotypic Pancreatic Tumor Spheroid Model and its Potential in Enhancing Response to Anti-PD-1 Treatment

Investigators: S. Vytheswaran, M. J. Szoo, H. Roberts, M. A. Saad, T. Hasan

Pancreatic ductal adenocarcinoma (PDAC) is an aggressive cancer characterized by desmoplasia, which promotes an immunosuppressed tumor microenvironment (TME). Photodynamic therapy (PDT) involves a photosensitizer that, upon light activation, generates cytotoxic reactive molecular species. Subtherapeutic PDT, or photodynamic priming (PDP), transiently alters the TME and enhances immune response via damage-associated molecular patterns (DAMPs), resensitizing treatment-resistant cancers to immunotherapy.

We hypothesize that a dose within the PDP range can sensitize desmoplastic PDAC spheroids to anti-PD1 immune checkpoint inhibition when co-cultured with peripheral blood mononuclear cells (PBMCs). Spheroids were generated by coculturing mCherry-expressing MIA PaCa-2 pancreatic cancer cells with EGFP-expressing pancreatic cancer-associated fibroblasts (PCAFs) at 1:3, 1:1, and 3:1 ratios. Selected spheroids received PDP (5 J/cm^2, 150 mW/cm^2), and Calreticulin expression was assessed via flow cytometry 24 hours post-treatment. PBMCs were added at an effector-to-target ratio of 2.5:1, with or without anti-PD1 at 40, 100, or 250 mg/mL. Spheroid viability was monitored via fluorescence intensity.

PDP was effective at inducing immunogenic cell death, as characterized by increased Calreticulin expression. Viability decreased across all desmoplastic conditions when co-cultured with PBMCs with and without anti-PD1 treatment showing concentration dependent cytotoxicity. Notably, PDP enhanced anti-PD1 efficacy even in spheroids with 75% PCAFs. These findings suggest that PDP improves immune checkpoint therapy response in desmoplastic PDAC. Future studies will investigate the roles of CD4+ and CD8+ T cells in mediating this response.

POSTER NUMBER:
43

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Mechanisms of resistance to first-line vs later-line alectinib in ALK-positive NSCLC

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Background: Next-generation ALK tyrosine kinase inhibitors (TKI) such as alectinib have supplanted crizotinib as first-line (1L) therapy for patients with ALK fusion-positive (ALK+) advanced/metastatic non-small cell lung cancer (mNSCLC). Post-progression biopsies can identify mechanisms of resistance and guide therapy selection. Most studies on ALK resistance evaluated pts who received alectinib as second- or later (2L+) line therapy after prior crizotinib, with limited data on resistance to 1L alectinib.

Methods: We retrospectively evaluated patients with ALK+ mNSCLC who received alectinib as 1L or 2L+ therapy after prior crizotinib and underwent post-progression tissue and/or plasma biopsies, analyzed by next-generation sequencing (NGS). Frequency of ALK resistance mutation(s), MET amplification, or histologic transformation was compared between 1L and 2L+ cohorts.

Results: We identified 125 patients with ALK+ mNSCLC who received alectinib as 1L (n=66) or 2L+ (n=59) therapy and underwent post-alectinib biopsies. In total, 162 post-alectinib specimens underwent NGS (tissue: n=86 [81 patients]; plasma: n=76 [68]); 24 (19.2%) patients had both tissue/plasma. ALK resistance mutations occurred at lower frequency in 1L vs 2L+ tissue cohort (1L: 42.2% vs 2L+: 66.7%, p=0.029), with similar findings with plasma. On tissue, MET amplification was numerically more frequent with 1L vs 2L+ alectinib (1L: 11.1% vs 2L+: 0%, p=0.062); histologic transformation occurred at similar frequencies (2.8-4.4%).

Discussion: In this largest series of alectinib-resistant biopsies to date, on-target resistance (ALK resistance mutation) was significantly less common when alectinib was used as 1L vs 2L+ therapy, underscoring the importance of identifying strategies to overcome off-target resistance to next-generation ALK TKIs.

POSTER NUMBER:
44

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Ultra-processed food and risk of early-onset colorectal cancer precursors among women: A prospective US cohort study

Investigators: C. Wang, M. Du, H. Kim, L. H. Nguyen, N. Khandpur, Q. Sun, X. Zong, E. Giovannucci, D. A. Drew, M. Song, Y. Cao, A. T. Chan

Background: Ultra-processed food (UPF) intake has increased steadily in parallel with the incidence of early-onset colorectal cancer (EOCRC) diagnosed before age 50 years. However, prospective data on the role of UPFs in early-onset colorectal neoplasia remain limited.

Methods: We examined data collected from 116,429 female nurses born between 1947–1964 in the Nurses' Health Study II and included participants who underwent at least one lower endoscopy from 1991 to 2015 before age 50 years. CRC precursors included conventional adenomas and serrated lesions. We defined UPFs based on the Nova classification. Generalized estimating equation logistic regression models were used to calculate multivariable-adjusted odds ratios (ORs) and 95% confidence intervals (CIs), accounting for known and putative risk factors including demographic, lifestyle, and family history.

Results: Among 30,762 women under age 50 years who had undergone at least one lower endoscopy, we documented 1,238 cases of early-onset conventional adenomas and 1,664 early-onset serrated lesions. Compared with women in the lowest quintile of UPF intake, women in the highest quintile had an increased risk of early-onset conventional adenomas (multivariable-adjusted OR=1.29; 95% CI: 1.07-1.56), including tubular (OR=1.25; 95% CI: 1.02-1.54), small (<1 cm) (OR=1.37; 95% CI: 1.08-1.75), and proximal adenomas (OR=1.41; 95% CI: 1.03-1.94). No statistically significant association was observed for early-onset serrated lesions (OR=1.11; 95% CI: 0.94-1.30).

Conclusion: These findings highlight a novel association of UPF consumption with increased risk of EOCRC precursors among women. These data support the potential of improving diet quality as a strategy to mitigate the rising burden of EOCRC.

Cancer

POSTER NUMBER:
45

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Defining the mechanisms and interactions of chemotherapy and immunotherapy in lung cancer

Investigators: C. Wong, J. Fang, A. Panda, C. Zielinski, I. Salinas, S. San Vicente, M. Sade-Feldman, N. Hacohen

Metastatic non-small cell lung carcinoma (mNSCLC) remains the leading cause of cancer-related mortality worldwide. For patients without actionable genetic driver alterations, the first-line most common treatment comprises chemoimmunotherapy using pemetrexed (Pem) and carboplatin (Carb) alongside anti-programmed cell death protein 1 (anti-PD-1) checkpoint blockade therapy (CPB). This combination leverages the cancer cell death mechanisms induced by Pem and Carb and reinvigorates CD8+ T cells by disrupting PD-1/PD-L1 interactions. However, only 20% of patients achieve durable clinical benefit. Prior studies do not provide deep mechanistic insights into how tumor cells become sensitive or resistant to Pem/Carb/anti-PD-1 CPB, so there is no hypothesis for this central problem in lung cancer. Here we show that Pem is the primary driver of cancer cell death sensitivity, while the Pem/Carb combination does not exhibit synergistic effects. Also, several immunogenic cell death (ICD) markers were induced across all NSCLC cell lines, regardless of their sensitivity or resistance to Pem/Carb. Lastly, we observed a significant delay in tumor growth in vivo following Pem/Carb/anti-PD-1 CPB treatment. However, all tumors eventually relapsed. These findings suggest a complex regulatory mechanism underlying cancer cell death, ICD, and immunity in Pem/Carb/anti-PD-1 CPB, warranting further investigation. Collectively, the results I aim to generate will provide critical insights into the mechanisms of sensitivity and resistance, ultimately guiding the development of targeted strategies to enhance the anti-tumor efficacy of chemoimmunotherapy in mNSCLC.

POSTER NUMBER:
46

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Preclinical investigation of a novel brain penetrant combination therapy targeting RAF and MEK for melanoma brain metastasis

Investigators: E. Yamazawa, N. Nayyar, C. Torrini, B. Marion, B. S. Zhang

Introduction: BRAF mutations are found in 50-55% of melanoma brain metastases. Current BRAF/MEK inhibitor's responses are not durable. Better therapies are needed with improved penetration of the blood-brain barrier. This study aims to evaluate the efficacy of two novel brain-penetrant inhibitors, KIN-7136 (MEK inhibitor) and KIN-8391 (RAF inhibitor), in mouse models of melanoma brain metastases driven by aberrant BRAF-MEK signaling. Methods: Cell Viability Assay was used for in vitro cell viability assays. Intracranial A375 melanoma models were generated in athymic nude mice to assess the pharmacodynamics, safety, and efficacy of combination therapy of KIN-7136 and KIN-8391. Results: In mice, the brain-to-plasma unbound partition coefficients (Kpuu) of KIN-7136 and KIN-8391 were 0.67 and 0.7 respectively, higher than the comparators binimetinib and belvarafenib, demonstrating improved brain exposure. The IC50s of KIN-7136/ KIN-8391 in melanoma cell lines were 27.0/36.5 nM in A375 (BRAF V600E), 78.6/35.4 nM in HMV2 (BRAF G469V), 183.0/699.0 nM in SK-MEL-2 (NRAS Q61R), and 53.9/110.0 nM in SK-MEL30 (BRAF D287H and E275K), respectively. KIN-7136 and KIN-8391 synergistically inhibited HMV2, SK-MEL-2, and SK-MEL-30 cells. Pharmacodynamic studies showed that both KIN-7136 and KIN-8391 suppressed phospho-ERK, a downstream component of BRAF-MEK signaling, in A375 xenografts in mice. Daily oral treatment with a combination of KIN-7136 and KIN-8391 was well-tolerated and extended overall survival to 64 days, compared to the control and monotherapies with KIN-7136 or KIN-8391 (28, 58, and 46.5, respectively) in the A375 intracranial tumor model. Conclusion: These preclinical data confirm the synergistic effect of KIN-7136 and KIN-8391.

Cardiovascular

POSTER NUMBER:
47

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Sex-specific Prognostic Value of Quantifying Coronary Plaque in Patients with Stable Chest Pain

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Background: Current cardiovascular (CV) risk assessment underestimates risk in women. It is unclear whether quantitative plaque analysis on coronary CT angiography (CCTA) improves sex-specific risk stratification.

Objectives: To assess whether plaque quantification on CCTA provides sex-specific prognostic value in patients with stable chest pain.

Methods: We analyzed patients from the PROMISE CCTA arm. A core lab quantified total plaque volume (PV, mm^3) and burden (PB, %), including calcified, noncalcified, and low-attenuation components. Sex-stratified multivariable Cox regression models and c-statistics evaluated whether plaque quantification improves risk prediction for major adverse cardiovascular events (MACE: death, myocardial infarction, or unstable angina) over a median follow-up of 26 months (IQR: 18–34). Models were adjusted for 10-year ASCVD risk, coronary artery calcium (CAC), obstructive stenosis (≥50%), and high-risk plaque (HRP) features.

Results: Among 4,267 patients, 2,199 (51.5%) were women (mean age 62.2±7.7 years). Women had lower ASCVD scores, lower CAC, less obstructive stenosis, less HRP, 72 mm^3 lower median PV and 12% lower median PB (all $P<0.001$). MACE occurred in 2.8% (121 events). In women, total and noncalcified PB independently predicted MACE (aHR: 1.27; 95% CI: 1.08–1.50, P=0.004 and aHR: 1.29; 95% CI: 1.07–1.55, P=0.007), but not in men. Adding PB improved risk prediction in women (AUC 0.71 to 0.75, P=0.017) but not in men (AUC 0.77 to 0.76, P=0.272).

Conclusions: Quantitative plaque assessment by CCTA improves risk stratification beyond traditional measures in women but not men, particularly through total and noncalcified plaque burden.

Cardiovascular

POSTER NUMBER:
48

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Sex-Based Outcomes in HeartMate 3 (HM3) Left Ventricular Assist Device (LVAD) Support

Investigators: A. M. Demelo, K. Drezek, T. Winship, E. Coglianese

There continues to be a disparity in the number of women receiving left ventricular assist device (LVAD) support. This may be due to heart failure type, but it may also be due to concerns about adverse outcomes; prior work has demonstrated worse neurological outcomes in women. This study aims to evaluate current sex-based outcomes in the modern era of fully magnetically levitated LVADs.

We performed a retrospective analysis of 29 female and 113 male patients from our institution implanted with a HeartMate 3 (HM3) LVAD between May 2016 and Aug 2023. The women in our study were significantly younger than men and had lower blood urea nitrogen, creatinine, hemoglobin, and uric acid levels at baseline. No other differences were observed between the two cohorts at baseline, including etiology of heart failure. Adverse events that occurred within 12 months of implant were categorized using INTERMACS (Interagency Registry for Mechanically Assisted Circulatory Support) definitions.

We show that at our institution, women with HM3 LVADs experience largely similar outcomes within the first year as men, with the exception of number of bleeding events. Women experienced more bleeding events on average (0.79 vs 0.43 events per person per year, p = 0.0427), but the time to first bleeding event was not significantly different. Importantly, there was no difference in neurological dysfunction events in women. Further work to understand the increased bleeding event burden is needed, but this work should reassure clinicians that newer generation VADs provide similar benefits to women as compared with men.

POSTER NUMBER:
49

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Obese HFpEF Patients Exhibit Distinct Augmentation Patterns of VO2 Components During Exercise

Investigators: I. Landsteiner, C. E. Newlands, C. Griskowitz, S. L. McGinnis, C. Prasad, A. Minasian, F. Moreno, G. D. Lewis

Obesity worsens exercise intolerance in heart failure with preserved ejection fraction (HFpEF) patients; however, limited understanding exists regarding how oxygen uptake (VO2) components—stroke volume (SV), heart rate (HR), and peripheral oxygen extraction (CavO2)—change during exercise. We hypothesized that obese and non-obese HFpEF patients would differ in VO2 augmentation patterns. We retrospectively analyzed 571 HFpEF patients who underwent invasive cardiopulmonary exercise testing at Massachusetts General Hospital. Minute-by-minute hemodynamic data (10 measures on average per patient) were collected, and VO2 components were assessed using time-based slopes. We calculated slopes in two phases: unloaded exercise and subsequent incremental exercise. Patients were categorized by body mass index (BMI; <30, 30–35, or ≥35 kg/m2). Those with higher BMI exhibited steeper increases in SV/time, HR/time, and CavO2/time during unloaded exercise but shallower slopes during incremental exercise compared with non-obese patients. In particular, the SV/time slope in the BMI ≥35 group was 6.92 mL/min (unloaded) vs. 0.95 mL/min (incremental). Furthermore, while the percentage change in SV during unloaded exercise was larger in the BMI ≥35 group (P<0.001), changes during incremental exercise were comparable across groups (P=0.803). Here we show that obese HFpEF patients have impaired VO2 component augmentation at higher workloads, underscoring the need for targeted strategies to improve functional capacity in this population.

Cardiovascular

POSTER NUMBER:
50

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Potential Role of Spectral Chest X-ray as a Screening Test for Coronary Artery Disease

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Background: Sensitive, accurate chest x-ray detection of coronary artery calcifications could provide a low-cost, low-radiation-dose, available, opportunistic screening tool for detecting unsuspected coronary artery disease (CAD) in urgent care settings

Objective: To compare the diagnostic performance of dual-energy, spectral chest X-ray (DEX-CXR) versus standard radiography (STD-CXR) for detecting coronary calcification

Materials and Methods: Fifty-two patients (63.9±18.6 years, mean+StdDev) underwent DEX-CXR and STD-CXR in an ED setting for non-cardiac indications. Three readers evaluated the CXRs for the presence/absence of coronary calcifications and rated confidence levels using a 5-point Likert scale for image quality. Interrater agreement was assessed using the interclass correlation (ICC). Sensitivity/accuracy were compared to a non-cardiac gated CT reference standard.

Results: Interrater ICC was 0.82 (95%CI: 0.74-0.89) for DEX-CXR and 0.63 (95%CI: 0.48-0.75) for STD-CXR assessment. Reader confidence was higher for DE-CXR than STD-CXR for all readers ($p<.05$, paired t-test). DEX-CXR significantly outperformed STD-CXR for the opportunistic detection of coronary calcifications, percent sensitivity/accuracy (mean+StdDev) = 75±0.06/87±0.05 for DEX-CXR, versus 28±0.06/67±0.07 for STD-CXR ($p<.01$, McNemars test).

Conclusion: This study demonstrates the potential of dual-energy, spectral CXR as a screening tool for coronary artery atheromatous calcification detection. If validated in larger studies, DEX-CXR may offer a cost-effective, low-radiation dose, widely accessible alternative to reference CT for opportunistic CAD screening in patients seeking care for other urgent/emergent conditions. For a subset of patients, this serendipitous detection will lead to early diagnosis and successful preventive treatment, ultimately curbing the impact of heart disease – the leading cause of mortality in the western world.

POSTER NUMBER:
51

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Comprehensive Mapping of Exercise Hemodynamic Responses and Multi-Organ System Reserve Capacity in HFpEF

Investigators: I. Landsteiner, T. Ikoma, C. Griskowitz, C. Prasad, A. Minasian, C. Newlands, F. Moreno, R. Malhotra, G. Lewis

Exercise effectively unmasks heart failure with preserved ejection fraction (HFpEF), with elevation in pulmonary capillary wedge pressure (PCWP) serving as the sole exercise-based diagnostic criterion. However, HFpEF encompasses physiologic abnormalities beyond elevated PCWP. We hypothesized that HFpEF patients have functionally and prognostically relevant physiologic deficits that are correlated with resting metabolite profiles.

Among 1,647 dyspneic patients referred for cardiopulmonary exercise testing with invasive hemodynamics, 840 met HFpEF criteria (left ventricular ejection fraction ≥50% plus ≥1: PCWP at rest ≥15 mmHg, elevated pro-BNP, prior heart failure event, or left atrial enlargement). We identified seven exercise deficits: decreased breathing reserve (VE/MVV >80%), elevated cardiac filling pressure (PCWP/CO slope >2), reduced heart rate augmentation (<80% predicted), decreased stroke volume (<80% predicted), increased pulmonary vascular resistance (PVR >1.5 WU at peak exercise), reduced peripheral oxygen extraction (<80% predicted), and increased metabolic cost of exercise (internal work >30 Watts). Metabolites were profiled using liquid chromatography-tandem mass spectrometry.

HFpEF patients (mean age 62±14 years, 54% female, BMI 31±7 kg/m^2) exhibited multi-organ deficits with significant interindividual variability. Compared to those without deficits, patients with ≥5 deficits had lower peak VO_2 (10.8±2.7 vs. 21.5±6.7 mL/kg/min) and higher risk for mortality and cardiovascular events (HR 3.84, 95% CI: 1.79-8.21, p<0.001). Among 441 metabolites, dimethylguanidino valeric acid (DMGV) explained the highest variance in peak VO_2 and correlated with all deficits except VE/MVV.

Here we show that multi-organ exercise deficits characterize HFpEF and predict outcomes, underscoring the need to move beyond PCWP alone to define exercise abnormalities and guide targeted interventions.

Cardiovascular

POSTER NUMBER:
52

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Opportunistic Assessment of Cardiovascular Risk using AI-Derived Structural Aortic and Cardiac Phenotypes from Non-Contrast Chest Computed Tomography

Investigators: D. W. Oo, A. Sturniolo, M. Jung, M. Langenbach, B. Foldyna, D. P. Kiel, H. J. Aerts, P. Natarajan, M. T. Lu, V. K. Raghu

Introduction: Primary prevention of atherosclerotic cardiovascular disease hinges on accurate risk estimation. However, necessary input variables to clinical risk algorithms (e.g., PCE, PREVENT) are often unavailable in the electronic health record, and information from routinely collected data (e.g., chest CT) may further improve performance. We test whether a risk prediction model based on structural features of the heart/aorta from chest CT has added value to existing clinical algorithms for predicting major adverse cardiovascular events (MACE).

Methods: We developed a radiomics-based LASSO model to predict MACE over 12-years of follow-up using 13,437 lung cancer screening chest CTs from the National Lung Screening Trial. Cardiac chamber and aorta segmentations were performed via an open-source deep learning tool, and radiomic shape features (e.g., sphericity) were extracted from each segmentation. We compared this model to the PCE/PREVENT scores in an external testing set of 4,303 individuals from Massachusetts General Hospital who were eligible for primary prevention.

Results: In the external testing set (n = 4,303; mean age 61.5 ± 9.3 years; 47.1% male), 8.0% had incident MACE over a median 5.1-years of follow-up. The radiomics risk score improved risk stratification and discrimination beyond the PCE (c-index 0.653 vs. 0.567, $p < 0.001$). Similar results were found when comparing to PREVENT. Left ventricular volume was most predictive of myocardial infarction, while aorta surface-to-volume ratio was most predictive of stroke.

Conclusion: Based on a single chest CT, a cardiac shape-based risk prediction model predicted MACE beyond standard-of-care algorithms and identified cardiac phenotypes most predictive of MACE.

Cardiovascular

POSTER NUMBER:
53

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Impact of concomitant surgery on left ventricular assist device (LVAD) outcomes

Investigators: B. G. Rees-Wiedemann, E. E. Coglianese, K. Drezek, T. R. Winship

Our aim was to determine the impact of concomitant surgery during LVAD implantation on health outcomes within one year post surgery in the modern era of VAD implant with a magnetically levitated LVAD (ML-LVAD). Data to date suggests that the impact of concomitant procedures on outcomes post-LVAD may add risk in the short term. However, correction of valve pathology or ischemia would be expected to reduce long term heart failure related complications post-LVAD.

From 2017-2023, 140 patients were implanted with a ML-LVAD at our center. 20% of these patients had concomitant surgery. Standard statistics were used to compare CPB time, ICU length of stay, total percent of time spent in hospital during the 1st year and 1st year adverse outcomes.

The concomitant surgery group was older and had higher CPB time ($p < 0.001$). Despite having a non-significant trend toward longer ICU length of stay; 10 vs 7 days respectively ($p=0.162$), the overall admitted hospital days in the year following ML-LVAD was not different between groups. There were no significant differences in the number of adverse events within the first year between the two groups. There was no difference in 1 year survival post ML-LVAD (log rank $p=0.2798$).

Despite the concomitant surgery group having a significantly longer CPB time, we found no difference in adverse outcomes, hospital stay or 1st year survival post ML-LVAD. Given the lack of evidence of a short-term “cost” to concomitant surgery, further work should be done to verify this and study long term impacts on survival.

POSTER NUMBER:
54

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Plasmalogen Control of Peroxisome Degradation Confers Protection from Ischemia

Investigators: M. Singh, S. Qayyum, G. Godoy, J. Benhalima, O. Seidel, H. Keshishian, A. Deik, C. B. Clish, S. A. Carr, G. A. Wyant

Peroxisomes are necessary for oxygen and lipid homeostasis and their dysfunction cause multiple human diseases. Peroxisome autophagy (pexophagy) is a key pathway to control peroxisome abundance, but the mechanisms that control peroxisome degradation in mammalian cells remain incompletely understood. Hypoxia has been shown to promote pexophagy through an unknown mechanism. Here, we identify a mechanistic link between hypoxia and peroxisomal plasmalogen metabolism in control of pexophagy. We identify Fatty acyl reductase 1 (Far1), the rate-limiting enzyme in peroxisomal plasmalogen synthesis, as a key component in oxygen control of peroxisome degradation. Biochemically, Far1 is peroxisomal membrane protein whose abundance is controlled via autophagy and binds ATG8-family protein LC3B in multiple tissues and in cells. Hypoxia promotes FAR1-dependent plasmalogen abundance and plasmalogen metabolism is both necessary and sufficient to control hypoxia-mediated pexophagy. In vivo, plasmalogens promote autophagy-dependent cardioprotection against ischemia reperfusion injury. This work reveals Far1 as a critical regulator of peroxisome homeostasis and connects peroxisomal plasmalogens to peroxisome degradation.

Cardiovascular

POSTER NUMBER:
55

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Endothelial cell dysfunction is detected in children with long COVID

Investigators: C. Steifman, S. Verma, B. Alvarez-Carcamo, L. M. Yonker

Introduction: Signs of endovascular disease, such as dizziness, dyspnea with exertion, and orthostatic tachycardia, are common in adults and children with long COVID. Long COVID-related endothelial dysfunction has been described in adults, often associated with Spike antigenemia. We sought to characterize endothelial dysfunction in children and determine whether intravascular Spike-activated neutrophils contribute to endothelial injury in pediatric long COVID.

Methods: Fibrin amyloid microclots in plasma were visualized with Thioflavin T, imaged on microscope slides, and analyzed. Angiogenesis, growth factor, and cardiovascular cytokine levels were quantified in plasma. Human Umbilical Vein Endothelial Cells (HUVECs) were cultured on transwells, treated with neutrophils activated by Spike-IgG immune complexes, then cell viability assays were performed.

Results: Plasma was collected from 46 children/young adults with long COVID and 15 healthy controls, with ages ranging from 6.4 to 22 years. Fibrin amyloid microclots were significantly increased children with long COVID ($p= 0.03$). Cytokine profiles revealed increases in angiogenesis related cytokines (HB-EGF and leptin) and serum amyloid P component with reductions of a2-macroglobin and L-selectin, suggesting dysregulated endothelial and clotting responses. Further, we found that in vitro, Spike alone resulted in minimal endothelial injury, whereas neutrophils activated by Spike-immune complexes elicited significant endothelial damage.

Conclusion: Our results suggest that endothelial cell dysfunction is present in pediatric long COVID and is, in part, related to Spike-activated neutrophils. Pediatric long COVID is understudied but offers an opportunity to define SARS-CoV-2-related endovascular injury in the absence of age-related cardiovascular history.

Cardiovascular

POSTER NUMBER:
56

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Epitranscriptional Regulation by METTL3 Protects Against Heart Failure with Preserved Ejection Fraction

Investigators: X. Xiao, K. Shimoda, S. Shen, Y. Zhang, A. Sugai-Munson, E. R. Jonas, I. S. Naarmann-de Vries, A. K. Chan, A. V. Ambardekar, M. R. Bristow, C. Castro, A. Singh, C. Zhou, J. Rhee, L. Xiao, C. Dieterich, F. Ichinose, J. Roh, H. Li

Background: Heart failure with preserved ejection fraction (HFpEF) is the most common form of HF. Despite the best available therapies, prognosis remains poor for many patients with HFpEF. N6-methyladenosine (m6A) is the most common form of messenger RNA modification in eukaryotes and has been implicated in cardiac development and disease. However, whether m6A plays a role in HFpEF is unknown.

Methods and Results: Methyltransferase-like 3 (METTL3) was the most downregulated m6A writer, at both the mRNA (by ~70%, $p<0.001$) and protein (by ~80%, $p<0.001$) levels, in hearts of patients with HFpEF compared to matched controls (n=12/group). Cardiac METTL3 protein expression was similarly downregulated by ~70% ($p<0.001$) in an established 'two-hit' (high fat diet + L-NAME for 15 weeks) mouse model of HFpEF, and associated with cardiac diastolic dysfunction, decreased contractile reserves, and increased fibrosis. These HFpEF phenotypes were further exacerbated in two-hit mice with cardiomyocyte (CM)-specific METTL3 knockout. Conversely, cardiac METTL3 overexpression (via an AAV9 encoding METTL3 driven by CM-specific promoter cTnT) improved cardiac diastolic function, increased contractile reserves, and reduced fibrosis in two-hit mice. CM-specific METTL3 overexpression notably induced similar effects on cardiac diastolic function and fibrosis in a distinct pressure-overload obese mouse model of HFpEF.

Conclusions: Cardiomyocyte (CM) METTL3 deficiency is part of the causal pathobiology of HFpEF and its CM-specific induction is sufficient to improve cardiac diastolic function and adverse remodeling in HFpEF. These findings identify METTL3 as a promising therapeutic target for HFpEF.

Child and Adolescent Health

POSTER NUMBER:
57

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Understanding the Role of Compression and Inflammation in the Formation of Pulmonary Hypoplasia Induced by Congenital Diaphragmatic Hernia

Investigators: O. M. Dinwoodie, X. Ai

Congenital diaphragmatic hernia (CDH) occurs due to improper diaphragm development, leading to the displacement of abdominal organs into the thoracic cavity and pulmonary hypoplasia. Only a small subset of patients exhibits chromosomal abnormalities or damaging genetic variants; thus, the precise etiology of CDH remains unclear. A conserved feature of CDH is mechanical compression of the fetal lung, causing pulmonary hypoplasia, which can be reversed by tracheal occlusion in sheep models. However, the pathological effect of compression is not well understood, limiting the progression of treatment options. Here, using a variety of CDH models including patient-derived cell cultures, sheep surgical models, rat nitrofen models and a novel 3D organoid culture method, we present a new mechanism for the etiology of CDH. We show that compression causes decreased nuclear localization of YAP (Yes-associated protein) in the airway epithelium, leading to heightened NF-κB-mediated inflammation. We identify a pathological role of the immune population, as upregulated epithelial IL33 leads to alveolar macrophage production of IL-1β, which, in turn, affects cell differentiation. Furthermore, we characterize patient-derived cell lines as heterogeneous, with varying severity linked to specific genetic alterations in combination with a 'memory' of mechanical compression. This finding challenges the traditional 'two-hit hypothesis' of CDH, suggesting that mechanical compression alone may be sufficient to initiate the condition. Our results exhibit the critical interplay between compression, YAP and NF-κB in the development of lung hypoplasia in CDH. Our proposed mechanism presents promising targets for therapeutic strategies, addressing a devastating condition that currently lacks effective treatment options.

Child and Adolescent Health

POSTER NUMBER:
58

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Projecting lifetime HIV-related healthcare costs for youth with HIV in the United States

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Background: Youth with HIV (YHIV) in the United States (US) face unique challenges to antiretroviral therapy (ART) adherence and care engagement. Understanding healthcare costs is important both for healthcare payers and to evaluate the economic impacts of youth-focused interventions to improve health outcomes.

Methods: Using the CEPAC-Adolescent microsimulation model, we simulated cohorts of YHIV 13-24y in care and prescribed ART at model start. Inputs were derived from published literature, including $80/outpatient visit, $3,200/inpatient day, $700/emergency department visit, and ART costs: $2,200-$4,700/month. We project life-months/person and population-level (n=30,782) lifetime HIV-related healthcare costs (discounted 3%/year) from a healthcare payer perspective. Inputs varied in sensitivity analyses include CD4, care engagement, and ART prices.

Results: YHIV were projected to live 47.4 life-years/person after model start (undiscounted), with discounted lifetime HIV-related healthcare costs of $728,000/person. Overall, this population would accrue $22.4 billion in discounted lifetime HIV-related healthcare costs. Monthly costs would depend primarily on CD4 count and would be highest during time spent at lower CD4s: $2,450/month/person (CD4 >500 cells/mm3) to $6,000/month/person (CD4 <50 cells/mm3). ART medications would comprise most costs (69%), followed by routine HIV-related clinical care (24%); applying generic ART prices could reduce total lifetime costs by 58% ($307,000/person).

Conclusions: We projected that US YHIV currently aged 13-24 in care would incur over $20 billion in lifetime HIV-related healthcare costs. Efforts to decrease the price of ART, as well as interventions to improve HIV care engagement and support consistent ART use, could reduce HIV care costs and improve health outcomes for YHIV.

Child and Adolescent Health

POSTER NUMBER:
59

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Targeted Physical Activity Intervention to Decrease PCOS Risk in Girls: A Pilot Study on Feasibility and Timing of Intervention

Investigators: M. Trujillo, R. Whooten

Background: Polycystic Ovary Syndrome (PCOS) is a common endocrine condition among women and is associated with risk for cardiometabolic disease. While early signs of PCOS appear in early adolescence and may be reduced with lifestyle intervention, little is known about the specific role of physical activity (PA) in PCOS prevention as well as the optimal timing and strategies for intervention.

Objective: We are conducting a small-scale pilot study of a PA intervention for girls aged 8-14 years who are at risk for PCOS to examine intervention delivery, feasibility, acceptability, and recruitment strategies.

Methods and Preliminary Results: We conducted two rounds of an abbreviated pilot intervention with small improvements between rounds. We enrolled n=3 caregiver-daughter dyads each round with mean (SD) child age 10.7 (2.1) years and 5/6 participants with a family history of cardiometabolic disease or PCOS. At baseline, 5/6 girls reported <4 days vigorous exercise in the prior week. The intervention consisted of 2 health coaching visits at weekly intervals (5/6 and 6/6 completed in Rounds 1 and 2, respectively), as well as daily text or email messages (14/14 delivered in both rounds; 38% and 69% completion in Rounds 1 and 2, respectively). Of follow-up survey respondents, 3/3 parents and 2/2 children rated the intervention feasible and acceptable.

Conclusions: Preliminary findings suggest success in enrolling the target population, intervention feasibility and acceptability, and improved intervention delivery in Round 2. A third round will further optimize the intervention and lead to a larger pilot trial of a PA intervention.

POSTER NUMBER:
60

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Unravelling Polygenic Risk and Environmental Interactions in Adolescent Polysubstance Use: a U.S. Population-Based Observational Study

Investigators: D. Zhi, B. T. Sanzo, B. Cormand, D. H. Jung, J. Sui, R. Jiang, R. T. Liu, J. Roffman, M. Fava, E. Evins, S. Hadland, J. Gilman, P. H. Lee

Thank you to the research participants and employees of 23andMe, Inc. for making this work possible.

Background: Polysubstance use (PSU), defined as the use of multiple psychoactive substances, has serious health consequences, with prevalence rising from early adolescence to adulthood, and is common among those who develop substance use disorders. We aimed to investigate how genetic susceptibility, and environmental exposures jointly influence adolescent PSU initiation.

Methods: Data were obtained from 11,868 adolescents aged 11-15 years old from the Adolescent Brain and Cognitive Development study. PSU was defined through interviews and toxicology. We examined the association of addiction genetic risk, derived from GenomicSEM analysis, environmental factors, and their interactions, with PSU initiation while controlling for multiple covariates.

Outcomes: Our sample comprised 7,898 adolescents (mean age 12.9 [0·6] years; 4,150 [53%] male participants). Overall, 541 (6.8%) had initiated single substance use (SSU), and 162 (2.1%) reported PSU. In the European group, general addiction risk for substance use disorders was significantly associated with PSU but not with SSU. Maternal substance use and peer victimization posed the highest risk for PSU, while planned pregnancy and positive family dynamics served as protective exposures. Notably, gene-environment interaction analyses revealed that peer victimization (odds ratio [OR]=2.4, 95% CI=1.4–4.2), maternal substance use (OR=2.1, 95% CI=1.2–3.6), and substance availability (OR=2.3, 95% CI=1.3–3.9), were significant at a high genetic risk level but weak or negligible at a low genetic risk level (all $p < 0.05$), in conferring risk for PSU.

Interpretation: This study underscores the importance of identifying high-risk individuals early and implementing tailored interventions to mitigate the risk of escalating substance use behaviors.

Computational/Bioinformatics, AI

POSTER NUMBER:
61

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Precision timing and dosing of preemptive add-on prophylactic medication against severe acute graft-versus-host disease: a prospective interventional trial of a machine learning model

Investigators: **Y. Cao, J. Chen, E. Jiang**

Severe (grade 3 – 4) acute graft-versus-host disease (aGVHD) remains a serious risk after haematopoietic cell transplants from haploidentical (Haplo) or HLA-mismatched unrelated (MMUD) donors. We calibrated a previously developed machine learning model, dynamic aGVHD Onset Anticipation Tianjin (daGOAT), integrated it into the posttransplant patient care pathways, and prospectively tested the model in 115 Haplo or MMUD transplants for precision timing and dosing of adding low-dose ruxolitinib based on early detection of aGVHD severity-associated changes in 141 dynamic co-variates (ClinicalTrials.gov, NCT05600855). Compliance with model-specified timing and dosing of ruxolitinib was 88% (n = 52) in the 59 subjects predicted to be at risk for imminent severe aGVHD. Total incidence of severe aGVHD in the prospective experimental cohort, the pre-specified primary endpoint, was 6% (7/115), significantly lower than that in matched controls (16% [46/280]; P = 0.008). 100-day GVHD-free relapse-free survival was 92% (95% confidence interval [CI], 87 – 97%; hazard ratio = 0.39), significantly better than that in the controls (81% [95% CI, 77 – 86%]; P = 0.007). Deployment of daGOAT did not lead to increased incidence of ruxolitinib-associated adverse events. Survey of the 62 participating clinicians indicated that overall the model was well-received by the clinicians; however, many were concerned about the need to monitor the safety of ruxolitinib. In conclusion, our study suggests the feasibility of using a machine learning model to guide precision timing and dosing of preemptive intervention against severe aGVHD.

POSTER NUMBER:
62

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Temporal Learning with Dynamic Range (TLDR) for multi-exposure, multi-treatment event predictions in electronic health records

Investigators: **J. Cheng, J. Hugel, H. Estiri, J. G. Klann**

Electronic health records (EHRs) are vital for observational research, offering rich, temporally relevant data but presenting challenges such as temporal misalignment and asynchronous event logging. Despite these issues, the sequential order of clinical events is highly predictive for chronic conditions like diabetes. Leveraging this temporal dimension can enhance the accuracy of clinical predictions and decision-making through machine learning.

We introduce the Temporal Learning with Dynamic Range (TLDR) algorithm, which improves feature categorization and aggregation by utilizing a dynamic window approach to capture temporal patterns accurately. This method classifies encounters into ‘history’, ‘past’, and ‘last’ categories based on their timing relative to initial and final exposures. We applied TLDR to predict Post-acute Sequelae of COVID-19 (PASC), using data from the Precision PASC Research Cohort (P2RC) at Mass General Brigham.

The study involved data from over 70,000 patients across eight Massachusetts health facilities. We evaluated the TLDR algorithm against traditional atemporal aggregation methods using gradient boosting, random forests, and boosted generalized linear models across various data levels. The TLDR method significantly outperformed the traditional approach, with average Area Under Curve (AUC) scores exceeding 0.9 compared to the benchmark’s 0.64. Statistical analysis confirmed the superior effectiveness of incorporating dynamic temporal adjustments.

These results underscore the benefits of the TLDR approach in enhancing predictive accuracy for PASC, highlighting the importance of integrating temporal data into feature engineering for improved clinical decision-making.

Computational/Bioinformatics, AI

POSTER NUMBER: **63**

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A mechanistic model of brain necrosis progression based on vascular heterogeneity

Investigators: N. Cogno, K. D. Shah, F. Ehret, C. Beekman, H. A. Shih, H. Paganetti, I. Chamseddine

Despite advancements in radiotherapy (RT), symptomatic brain radionecrosis (RN) affects approximately 5% of brain tumor patients. Often mistaken for tumor pseudo-progression, RN leads to irreversible impairments in cognition, hearing, and vision. Conventional risk assessment based on treatment-specific parameters, such as absorbed dose and linear energy transfer, has proven inadequate for reliably predicting RN onset. Further complicating risk prediction, necrotic volumes often expand beyond their original location by the time of diagnosis and imaging. Evidence suggests that vascular damage is the primary driver of RN progression, and patient-specific vascular heterogeneity may obscure treatment effects. To quantify RN risk, its progression must first be modeled.

Here, we present a mechanistic three-dimensional cellular automaton model to simulate RN progression after detection, using only vascular features. Trained on longitudinal patient data (N=6, steroid-treated patients were excluded) with Bayesian methods, the model incorporates a synthetic vessel tree aligned with each patient's MRI to account for anatomical boundaries and vascular heterogeneities. Each millimeter-scale model unit is characterized by capillary length density, a proxy for blood flow, adjusted inversely with the distance from major vessels. Inferred posterior parameter distributions encapsulate population-level knowledge, while comparisons of predicted probability heatmaps against ground truth data demonstrate strong predictive performance, with areas under the receiver operating characteristic curve of 0.87, 0.92, and 0.95 across three independent necrotic lesions.

These findings highlight the importance of incorporating vascular metrics into RT treatment planning to mitigate RN risk and improve patient outcomes. This predictive framework may extend beyond radiation-induced RN to other therapy-related toxicities.

POSTER NUMBER: **64**

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RoentMod: Synthetic Pathology on Chest X-Rays Reveals Potential for Bias in Image Interpretation Models

Investigators: L. H. Cooke, M. Jung, J. Brendel, B. Foldyna, M. T. Lu, V. K. Raghu

Due to an abundance of chest x-ray images, deep learning models can efficiently identify chest x-ray pathology. Despite this success, there is limited impact on clinical practice due in part to a lack of understanding of and trust in how models make decisions, preventing clinicians from effectively collaborating with models. This work introduces Roentmod: a generative deep learning model to alter an existing chest x-ray with a prompt describing radiological pathology like cardiomegaly or pneumonia. Roentmod takes an existing chest x-ray image and a text description of pathology as input and outputs a new chest x-ray of that individual with the indicated pathology. We then applied Roentmod to explore whether publicly available diagnostic models are sensitive to the addition of other pathology using Roentmod's synthetic scans.

Here we show that Roentmod is consistent and accurate in modifying an existing chest x-ray to add a pathology while preserving unrelated anatomy, with success rates of 84% for pulmonary edema, 88% for cardiomegaly, 92% for pleural effusion, and 98% for pneumonia using the radiologists' read as the reference standard. Using Roentmod-generated chest x-rays, we showed that diagnostic deep learning models claiming to identify pathology from input chest x-rays likely use anatomical features other than the pathology itself to make their predictions. In future work, we will assess whether fine-tuning diagnostic models on synthetic scans improves generalization performance, radiology education, and interpretability of other image interpretation models.

Computational/Bioinformatics, AI

POSTER NUMBER:
65

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A Novel Application for Evaluating Treatment Efficacy in ALS Using Real-World Data

Investigators: J. A. Geller, A. J. Berger, M. C. Bind, A. V. Sherman, ALS Natural History Consortium

Background: Amyotrophic Lateral Sclerosis (ALS) is a fatal, neurodegenerative disease with limited successful phase 3 trials. Propensity score matching is a causal inference method that mimics the design of randomized controlled trials using observational data, enabling cost-effective treatment assessments.

Objectives: We investigate whether baseline function measured by ALSFRS-R has a positive effect on 18-month survival and whether 18-month survival is different by sex.

Methods: Data are from the ALS Natural History Consortium and include over 2,700 ALS individuals. Individuals without missing data were matched using baseline covariates. Survival differences were evaluated using permutation tests. We used principal stratification to handle lost to follow-up. The process was repeated with multiply imputed data.

Results: The permutation test p-values using 100,000 permutations of the treatment assignment are $p \approx 0.62$ (Sex) and $p < 0.00001$ (ALSFRS-R) for individuals not-lost to follow up and $p \approx 0.67$ (Sex) and $p < 0.00001$ (ALSFRS-R) on stratified individuals. The p-values from the sensitivity analysis are $p \approx 0.69$ (Sex) and $p < 0.00001$ (ALSFRS-R) for individuals not lost to follow up and $p \approx 0.67$ (Sex) and $p \approx 0.0004$ (ALSFRS-R) on stratified individuals.

Conclusions: Our findings suggest that baseline function has a positive effect on 18-month survival, while we could not reject the null hypothesis for sex. These results align with existing research and illustrate how to use propensity score matching in ALS research. This approach could be valuable in re-evaluating previously failed trials, determining treatment efficacy in broader populations, or over longer periods.

POSTER NUMBER:
66

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Markov Field Network Model of BMI-Driven Protein Networks and Preterm Birth Subtypes in 2nd Trimester Cohorts

Investigators: P. A. Lopez Zapana, C. A. DeBolt, V. R, A. G. Edlow, M. A. Elovitz, D. A. Lauffenburger

Pre-pregnancy Body Mass Index (BMI) is associated with preterm birth (PTB), but the underlying mechanisms linking BMI to PTB, and how these differ by PTB subtype, remain unknown. PTB has two subtypes: spontaneous PTB (sPTB), caused by the unexpected labor onset, and medically indicated PTB (mPTB), which results from obstetric intervention due to maternal or fetal complications. In this study, we analyzed the levels of 6153 proteins in maternal plasma collected during the 2nd trimester from 100 pregnant individuals (N=30 for sPTB, N=30 for mPTB, and N=40 patients who delivered at term without any medical or obstetrical comorbidities). 2nd trimester maternal plasma was selected given the need to identify predictive biomarkers prior to the onset of preterm labor. We applied concepts from Markov Field network modeling to eliminate spurious interactions and find critical protein intermediates linking BMI-to-mPTB and BMI-to-sPTB. Differential network analysis of the two networks revealed distinct patterns of protein interactions specific to each PTB subtype. For example, in the BMI-to-mPTB network, we identified that BMI directly influenced proteins related to inflammation dysregulation, which were linked to mPTB. In contrast, in the BMI-to-sPTB network, we identified a direct influence of BMI on proteins associated with nutrient metabolism and epithelial integrity, which in turn were highly linked to sPTB. Overall, we show the importance of the 2nd trimester for identifying mechanisms underlying PTB and highlight molecular pathways linking BMI to PTB subtype, with implications for biomarker discovery and targeted interventions.

Computational/Bioinformatics, AI

POSTER NUMBER:
67

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Using Large Language Models to identify cutaneous immune-related adverse events in response to immunotherapy.

Investigators: C. Lu, G. Wan, S. Khattab, Y. R. Semenov

Cutaneous immune-related adverse events (cirAEs) are the most common immune checkpoint inhibitor (ICI) toxicities and potential predictors of therapeutic response. However, identifying cirAEs is challenging due to varied presentation and the lack of diagnostic codes, requiring manual chart review. This study explores the use of Large Language Models (LLMs) to automatically identify cirAEs from unstructured outpatient and inpatient clinical notes. Unlike previous work focused solely on structured inpatient notes, we address the novel challenge of analyzing the much more heterogeneous outpatient documentation where most cirAEs would be documented.

Using a multi-institutional cohort from Mass General Brigham and Dana-Farber Cancer Institute (2015–2022), we evaluated LLaMa-3.1, Gemma-2, Qiwen-2.5, and GPT4o in a Retrieval Augmented Generation (RAG) system with a hybrid keyword and vectorized semantic search and example-based fine-tuning. In a test on 100 patient notes, GPT4o achieved the highest sensitivity (0.82) and specificity (0.88), outperforming LLaMa-3.1 (0.55/0.63), Gemma-2 (0.68/0.64), and Qiwen-2.5 (0.23/0.94).

The LLMs analyzed 100 patient notes in just 45 minutes (27 seconds per patient), a significant improvement over the 15 minutes typically required per patient for manual review. With further optimization, LLMs have the potential to replace manual annotation entirely, requiring a human in-the-loop only for final verification. This approach provides tremendous time savings that could unlock valuable data from unstructured clinical notes, enabling further research that could advance our understanding of cirAEs, their clinical implications, and biological mechanisms.

POSTER NUMBER:
68

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Adaptive Risk Estimation System (ARES): A Next-Generation Early Warning System for Real-Time Patient Care

Investigators: P. Renc, M. Grzeszczyk, N. Oufattole, D. Goode, Y. Jia, S. Bieganski, M. McDermott, J. Was, A. Samir, J. Cunningham, D. Bates, A. Sitek

Healthcare systems face persistent challenges in identifying patients at risk for serious complications, partly due to limited use of the vast and complex data in electronic health records. Traditional scoring methods often rely on static measurements and fixed thresholds, making them inflexible and less accurate. We developed a novel transformer-based platform called the Adaptive Risk Estimation System that analyzes each patient's health information as a continuous timeline of clinical events. By drawing on more comprehensive and chronologically structured data, it generates dynamic, real-time risk estimates for critical outcomes such as intensive care admission or extended hospital stays.

Here we show that our system outperforms conventional models by adapting to each patient's evolving condition and integrating diverse types of medical data. Its ability to update risk estimates when new information becomes available offers a level of personalization and reliability not found in existing methods. Additionally, the system provides patient-specific explanations of its predictions, helping clinicians identify the medical events that contribute most to elevated risk. These features enable more timely interventions, potentially improving patient outcomes and reducing healthcare costs. Our findings suggest that this approach could be applied broadly, as it is compatible with varied healthcare data and can be extended to predict other important clinical events. Ultimately, we believe our framework offers a transformative tool for patient care, blending advanced machine learning with practical insights tailored to individual patient needs.

Computational/Bioinformatics, AI

POSTER NUMBER:
69

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AI & Big Data in MRI: A Dual Study on Image Classification and Intensity Normalization for Brain Imaging

Investigators: P. Salome, H. Chamseddine, I. Paganetti

Purpose/Objective: This work aims to address MRI processing standardization in radiomics through two studies: developing a multimodal-based classifier to manage DICOM metadata inconsistencies and investigating the impact of intensity normalization methods on MR sequences in multicentric datasets.

Materials/Methods: The study assessed data from three high-grade glioma cohorts, using C1 for training and C2 and C3 for testing. A multimodal sequence classification pipeline was developed using deep convolutional neural networks and natural language processing, distinguishing between 24 classes in brain MRI datasets. The impact of 15 different intensity normalization methods on overall survival radiomics models was studied by extracting sequence-specific significant features from tumor volumes. Survival analyses were conducted using Cox proportional hazard and Poisson regression models, with performance evaluated through 10-fold cross-validated concordance index, mean square error, and Akaike information criterion.

Results: The classifiers achieved 96.1% accuracy in identifying physics-based MR sequence classes, demonstrating distinguishable characteristics between sequence subtypes. Manual review revealed motion artifacts and anatomical distortions caused by large tumors in the misclassified images. The impact of intensity normalization methods on survival predictions varied significantly across different MR sequences, demonstrating sequence-specific sensitivity to normalization method. After controlling for normalization-impacted features, mean decreases of 0.17 in concordance index and 0.15 in mean square error were observed across all sequences.

Conclusion: This work highlights the need for physics-informed subtype classification and sequence-specific intensity normalization methods guided by relevant clinical and imaging characteristics.

Computational/Bioinformatics, AI

POSTER NUMBER:
70

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An Agentic AI Workflow for Detecting Cognitive Concerns in Real-world Data

Investigators: L. Wang, P. Fard, V. Moura Junior, D. Blacker, J. S. Haas, C. Patel, S. N. Murphy, L. M. Moura, H. Estiri

Early detection of cognitive concerns is critical but often hindered by subtle symptoms resembling normal aging. Large language models (LLMs) offer scalable screening solutions, and multi-agent systems enhance task automation. This study develops and evaluates an agentic workflow using task-specific agents to identify cognitive concerns in clinical notes.

Using a curated cohort at Mass General Brigham, two datasets of 100 patients each were extracted for prompt development and validation. LLaMA 3 8B, an open-source LLM developed by Meta AI, was used to ensure data privacy. The agentic workflow involved six specialized agents that iteratively refined the prompt to optimize sensitivity and specificity until predefined thresholds were met. The standard operating procedure (SOP) from the previous study provided the guidelines for identifying cognitive concerns.

The study analyzed over 2,000 notes for prompt development and roughly 1,000 for validation. The agentic workflow performed well on the development dataset, achieving an F1-score of 0.90, with a sensitivity of 0.84 and perfect specificity (1.0). However, performance dropped significantly on the validation dataset—by 14% in F1-score and 23% in sensitivity.

Our findings highlight the potential of LLM in detecting early cognitive concerns and point to the promise of agentic workflows as scalable tools for clinical screening. However, the limited generalizability underscores the need for further refinement to reduce overfitting when applied to diverse datasets. This study connects technical innovation with clinical relevance, offering practical insights into using LLMs in healthcare.

POSTER NUMBER:
71

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A natural language processing algorithm accurately classifies diverticulitis and associated complications and predicts the risk of long-term outcomes

Investigators: W. Ma, P. K. Challa, J. M. Downie, D. Sikavi, T. G. Simon, H. Khalili, A. R. Kambadakone, A. N. Ananthakrishnan, L. L. Strate, A. T. Chan

Diverticulitis is a highly common gastrointestinal condition requiring hospital encounters, but predicting recurrence or future complications at the first episode remains challenging. Diagnostic codes are effective in identifying diverticular disease overall. However, they lack precision to distinguish between subtypes. Here, we developed and validated a natural language processing (NLP) algorithm to classify diverticulitis and associated complications using information from patients data with a diagnosis code for diverticular disease and abdominopelvic computed tomography (CT) reports from the Research Patient Data Registry of the Mass General Brigham. We subsequently investigated the associations between disease severity at first diagnosis based on NLP-derived features and the risk of recurrent diverticulitis requiring hospitalization using a Cox proportional hazards regression model adjusting for age, sex, race, and obesity. Our NLP algorithm achieved positive and negative predictive values of 88.2% to 100% for all classification concepts. Among 16,675 patients with CT-confirmed first diagnosis, 3,284 hospitalizations for recurrent diverticulitis were documented over 130,789 person-years of follow-up. NLP-derived complications were significantly associated with the incidence of recurrent diverticulitis requiring hospitalization. Compared to uncomplicated diverticulitis, the multivariable-adjusted hazard ratio for recurrence was 1.47 (95% confidence interval [CI], 1.23-1.77) for mildly complicated, 3.39 (95% CI, 3.15-3.65) for severely complicated, and 2.92 (95% CI, 2.42-3.51) for chronic complications. In conclusion, our NLP algorithm accurately classifies diverticulitis subtypes and complications from CT free-text reports, facilitating the construction of a large and high-quality diverticulitis cohort and highlighting an increasing risk of recurrent diverticulitis corresponding to the severity of the initial diagnosis.

Endocrinology

POSTER NUMBER:
72

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Lower oxytocin levels are associated with increased anxiety and depressive symptoms in adults with obesity

Investigators: T. Bitar, F. Galbiati, F. Plessow, C. S. Carter, S. Nazarloo, E. Asanza, S. E. Smith, E. Lawson

Background: Obesity increases the risk for anxiety and mood disorders. Oxytocin (OXT) is an anorexigenic neurohormone under investigation for obesity treatment that improves anxiety and mood in animals and humans. Further, our trial of 8-weeks intranasal OXT resulted in improved mental health-related quality of life in adults with obesity, but the effect of endogenous OXT on anxiety and mood is not fully understood. We examined the relationship between fasting OXT levels and anxiety and depressive symptoms in adults with obesity. We hypothesized that OXT levels would be negatively correlated with anxiety and depressive symptoms.

Method: Cross-sectional study in 61 adults with obesity (53.8% female, age [mean(SD)] 33.7(6.2) years, BMI 37.0(4.9) kg/m2). Fasting plasma OXT levels were drawn in the morning. Beck Depression Inventory-II (BDI-II), State-Trait Anxiety Inventory (STAI) Trait, and Liebowitz Social Anxiety Scale (LSAS) questionnaires were used to assess symptoms of depression, anxiety and social anxiety, respectively. Higher scores indicated more severe symptoms.

Result: Mean(SD) self-reported symptoms of depression [BDI-II total score 4.79(6.38)] and anxiety [STAI-Trait score 34.98(8.28)] were in the normal range. LSAS total score was 35.30(27.37), consistent with mild symptoms of social anxiety. Plasma OXT levels were negatively correlated with BDI-II (rho = -0.34; p = 0.018) and LSAS (rho= -0.37; p = 0.027) scores. OXT did not correlate with STAI-T (rho= -0.12; p=0.355).

Conclusion: Lower OXT levels were related to worse depressive and social anxiety symptoms in adults with obesity with no psychiatric comorbidities. Investigation of whether endogenous OXT mediates psychological symptoms in obesity is warranted.

Genetics & Genomics

POSTER NUMBER: **73**

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'LOMARS' Missense Mutation Rescues the Huntingtin Null Allele in Mice

Investigators: B. Demelo, W. Kim, T. Gillis, M. Kovalenko, E. Elezi, K. Lee, I. S. Seong, M. MacDonald

Lopes-Maciel-Rodan Syndrome (LOMARS) is a severe congenital neurodevelopmental disorder affecting rare individuals with bialellic hypomorphic variants of the huntingtin gene. Huntingtin protein deficiency has been shown to cause severe developmental abnormalities in mice and humans, and complete deactivation of huntingtin is early embryonic lethal. Novel mice possessing the LOMARS missense mutation were generated to further study the effects of low huntingtin levels, an important line of investigation in Huntington's Disease therapeutic efforts in which huntingtin-lowering is a prominent strategy. LOMARS mice were crossed with huntingtin knock-in mice, which possess CAG expansions in exon 1 of the gene, characteristic of Huntington's Disease. Here, the murine LOMARS allele is shown to rescue huntingtin nullizygous lethality, with and without the expanded CAG tract. However, LOMARS/null mice are underrepresented compared to their littermates, with the most extreme effect correlating with the longest CAG expansion. This confirms previous findings that suggest there is some threshold of huntingtin protein required for normal development in utero. By quantifying the amount of huntingtin protein produced by these novel alleles, we gain deeper insight into what that threshold may be. Analysis of brain and peripheral organ morphology in aged mice illustrate potential effects of huntingtin deficiency at the macroscopic level. These results may provide important clues pertaining to huntingtin normal function and how it is interrupted in Huntington's Disease patients.

POSTER NUMBER: **74**

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Improving the Precision of Single Base Genome Edits with Engineered CRISPR Base Editors

Investigators: M. A. Fallon, E. M. King, B. P. Kleinstiver

Adenine base editors (ABEs) are a CRISPR-based technology that can install targeted A-to-G DNA edits in living cells. ABEs are comprised of two main domains, a Cas9 enzyme that can be programmed with a guide RNA to target a specified DNA sequence, and an adenine deaminase that performs a chemical reaction on adenine bases within the target sequence. Recent engineering efforts have improved the efficiency and precision of ABEs while also minimizing the unintentional deamination of neighboring non-target bases. However, precision genome editing with ABEs requires careful positioning of the Cas9 domain near the target base to ensure the intended base is maximally accessible to the deaminase domain. While deaminases tethered to wild-type SpCas9 typically result in highly efficient base editing, they are restricted to target sites adjacent to NGG DNA sequences called protospacer adjacent motifs (PAMs). This constraint limits the scope of editable and correctable pathogenic mutations because canonical NGG PAMs are typically not available in the correct genomic locations. Here we sought to overcome this limitation by generating and testing ABEs comprised of engineered Cas9 enzymes that have relaxed or altered PAM preferences, serving to increase the diversity of genomic loci that are accessible to base editors. We demonstrate that ABEs leveraging engineered Cas9 enzymes are capable of efficient and specific base editing at target sites inaccessible to wild-type SpCas9. Together, our results support the use of engineered base editors to improve the precision of genome editing, with implications to broaden the utility of ABEs for therapeutic use.

Genetics & Genomics

POSTER NUMBER:
75

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Biomarkers for Somatic Instability of the CAG Repeat in Huntington's Disease

Investigators: P. Hornbostel, R. Mouro Pinto, M. Kesavan, A. Shahryari, S. Shibata, P. Seabra

Huntington's Disease (HD) is an autosomal dominant neurodegenerative disease, which is characterized by cognitive decline and motor incoordination. The pathogenesis of HD is affected by an inherited expanded CAG repeat in exon 1 of huntingtin protein (HTT). In healthy individuals, this repeat consists of <40 repeats. In affected individuals (>40 repeats) the repeat is prone to generational expansion, and expansion over an individual's lifetime (somatic expansion). The age of onset has been shown to be inversely correlated with CAG repeat length, supporting targeting somatic expansion as a therapeutic target for HD.

Somatic expansion occurs most severely in the brain, primarily affecting Medium Spiny Neurons (MSNs) in the striatum. It is important to have a biomarker for HD, for earlier diagnosis and as a measurement of efficacy of therapeutics in clinical trials. This tissue is not easily accessible as a biomarker for HD, so our aim is to find less invasive peripheral tissues as a biomarker for HD.

The aim of this study is to explore potential biomarkers of HD, such as blood and stool. Previous data from our lab show a positive trend in instability in stool over a mouse's lifetime. We plan to test this in a new mouse model of HD (Q140 mouse) and human stool, to show that CAG repeat instability in stool can be used as a biomarker for HD.

POSTER NUMBER:
76

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Using Polygenic Risk Scores to Predict Risk of Attention-Deficit/Hyperactivity Disorder and Disruptive Behavior in Youth

Investigators: M. Iorini, A. Doyle, M. DiSalvo, J. Wozniak, S. Faraone

Based on GWAS, polygenic scores (PGS) can quantify individuals' risk for a given construct and may eventually facilitate personalized care. In psychiatry, the largest GWAS have predominantly been based on single diagnoses, but GWAS of dimensional traits or comorbid disorders are promising for clinical translation. Comorbid disruptive behavior or aggression in ADHD confers additional risk for poor outcomes. This study examined whether PGSs based on smaller GWAS of ADHD plus disruptive behavior disorders (ADHD+DBD) and aggression were associated with relevant constructs over and above PGS from a larger GWAS of ADHD.

Participants included 434 Caucasian youths, aged 4 to 17. PGS were from recent GWAS of ADHD, ADHD+DBD, and aggression. First, we examined the association between PGSs and diagnostic groups stratified by the presence or absence of ADHD and/or DBD determined from diagnostic interviews. Second, we examined the association between PGSs and subscales from the Child Behavior Checklist. Analyses included multinomial logistic regression and truncated Poisson regression.

The ADHD PGS was significantly associated ($p<0.001$) with ADHD diagnostic groups regardless of DBD comorbidity, and the ADHD+DBD score did not explain additional variance in groups with DBD. The ADHD PGS was associated with attention problems, aggression, delinquent behavior, and anxious/depressed symptoms ($p<0.001$), and the aggression PGS did not explain additional variation.

Here we show that PGS from smaller GWAS of comorbid conditions and aggression did not add to prediction over and above PGS from a larger GWAS of ADHD. However, this latter score related to traits across diagnostic boundaries.

Genetics & Genomics

POSTER NUMBER:
77

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lncRNA-Mediated Heterochromatin Assembly

Investigators: J. S. Khanduja, R. I. Joh, M. M. Perez, J. A. Paulo, C. M. Palmieri, J. Zhang, A. Gulka, W. Hass, S. P. Gygi, M. Motamedi

Heterochromatin, an architectural feature of eukaryotic cells, is pivotal for genome organization, epigenetic gene silencing, cellular differentiation, and genome stability in human cells. Disrupted heterochromatin can lead to genomic instability and is thought to contribute to imprinting disorders and trinucleotide repeat expansion disorders in humans. The Suv39 family of proteins tri-methylate lysine 9 of histone H3 (H3K9me) for constitutive heterochromatin establishment at repetitive sequences in eukaryotes. However, how Suv39 proteins are nucleated at these repetitive sequences is not fully described. In the fission yeast, current models posit that Argonaute1-associated small RNAs (sRNAs) nucleate the sole H3K9 methyltransferase, Clr4/SUV39H, to pericentromeric repeats. Here, we show that in the absence of all sRNAs and H3K9me, the Mtl1 and Red1 core (MTREC)/PAXT complex nucleates Clr4/SUV39H at a heterochromatic long noncoding RNA (lncRNA), at which the two H3K9 deacetylases, Sir2 and Clr3, also accumulate by distinct mechanisms. Iterative cycles of H3K9 deacetylation and methylation spread Clr4/SUV39H from the nucleation center in an sRNA-independent manner generating a basal H3K9me state. The RNAi machinery augments and amplifies the Clr4/H3K9me signal at pericentromeres to establish heterochromatin. Overall, our data reveal an alternative axis for heterochromatin nucleation at the pericentromeres which employs lncRNAs and the RNA binding capability of MTREC, a Clr4-interacting complex, as specificity factors for Clr4 recruitment. The Clr4/SUV39H nucleation and spreading model proposed in the fission yeast could serve as a molecular blueprint for these steps in heterochromatin establishment in vertebrates.

POSTER NUMBER:
78

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Capturing time-varying childhood adversity exposures through DNAm profile scores to predict adulthood depressive symptoms

Investigators: K. Y. Law, J. Chen, A. Hüls, A. A. Lussier

Background: Childhood adversity is a potent risk factor for depression, and exposure during sensitive periods can magnify negative impacts on mental health. DNA methylation (DNAm) may biologically embed the effects of early-life exposures to influence later health outcomes. However, no studies have investigated whether the aggregated predictive power of epigenetic changes during sensitive periods can predict future psychopathology. Here, we developed timing-specific DNAm profile scores (MPS) of childhood adversity and investigated their ability to capture prior exposures to maternal psychopathology and predict future depressive symptoms.

Methods: Prospective measures of maternal psychopathology exposure (between 10w-5y), epigenome-wide whole-blood DNAm (5y) and SDQ internalizing symptom scores (8y) were collected from participants of the Drakenstein Child Health Study (DCHS, N=586). MPS were calculated from the effect sizes of an independent meta-analysis of time-varying maternal psychopathology and DNAm at 7-10y. The abilities of timing-specific (MPS-TS) and ever-exposed MPS (MPS-EVER) to capture maternal psychopathology exposure and predict internalizing symptoms were assessed via variance explained (R2) and covariate-adjusted OLS regressions.

Results: MPS-EVER was not associated with maternal psychopathology, whereas MPS-TS was positively associated with maternal psychopathology at age 1-3 (β=0.08; 95%CI=[0.03,0.14]; p=0.02; R2=0.3%), then negatively at age 3-5 (β=-0.12; 95%CI=[-0.21,-0.04]; p=0.002; R2=0.4%). Both MPS-EVER (β=-0.21; 95%CI=[-0.32,-0.14]; p=9e-07; R2=0.3%) and MPS-TS (β=-0.17; 95%CI=[-0.28,-0.05]; p=0.03; R2=0.1%) were negatively associated with internalizing symptoms at age 8 years.

Conclusions: Our findings suggest timing-specific MPS may be useful population-level biomarkers of early-life exposures and may help identify individuals at higher risk for psychopathology and adverse health outcomes resulting from childhood adversity.

Genetics & Genomics

POSTER NUMBER:
79

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CRISPR-Cas9-mediated Msh3 knockout in mice to assess impact on Huntington's disease phenotypes and therapeutic implications

Investigators: E. Oliver, M. Kovalenko, A. Jiang, N. Romano, B. Jones, F. Saif, V. C. Wheeler

Huntington's disease (HD) is a fatal, dominantly inherited neurodegenerative disorder caused by a CAG repeat expansion in the HTT gene, exhibiting characteristic neuropathology, with selective vulnerability of neurons in the striatum and cortex. The rate at which the CAG expands in somatic cells determines the rate of clinical onset, with strategies to slow somatic CAG expansion holding great promise as disease-modifying therapies that can act prior to onset. Several DNA repair genes, especially those involved in the mismatch repair (MMR) pathway, play a role in somatic expansion and modify disease course in patients. One of these encodes MSH3 that is required for somatic CAG expansion and is believed to preferentially recognize CAG loop-outs as part of the MutSβ heterodimer, initiating DNA repair process that leads to expansion. Thus, human genetic data and strong functional data make MSH3 a prime therapeutic target. Amongst MMR components, MSH3's oncogenic liability is low, enhancing its therapeutic potential.

Here, we have implemented CRISPR-Cas9 editing in HttQ111mice to knock out Msh3. We have used the PHP. eB AAV9 variant for systemic delivery to brain tissues at different ages to explore the potential of stopping somatic expansion at progressively later time points as a treatment for HD. We will investigate effects on phenotypic expression, specifically by assessing somatic instability, transcriptional dysregulation and huntingtin protein aggregation. Ultimately, this research aims to deepen our understanding of how targeting Msh3 could alter the trajectory of HD, and to provide insight into the influence of the timing of intervention on therapeutic effectiveness.

POSTER NUMBER:
80

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Defining the Landscape of Poison Exon Splicing Events in the Human Brain: Implications for Neurodevelopmental and Neurodegenerative Disorders

Investigators: P. Pigini, H. Lindmeier, Y. Jin, M. C. Silva, D. Gao, E. Morini

Poison exons (PEs) are highly conserved exon cassettes whose inclusion creates premature termination codons (PTCs) and triggers nonsense-mediated decay (NMD) of the mature transcript, therefore reducing protein expression. Despite their critical role in gene expression regulation, PEs have not been systematically annotated due to the lack of comprehensive approaches that utilize transcriptome-wide data. In this study, we investigated the role of PEs in the human brain and assessed the impact of pathogenic variants on their regulation. To delineate the full landscape of PEs in the human transcriptome, we included conserved (PhyloP score≥20) alternatively spliced exons with the ability to introduce PTCs. Our analysis identified 12,014 PEs in the human transcriptome. For each PE, we calculated the percent-spliced-in (PSI) value across tissues and developmental stages using GTEx and BrainSpan data. We identified 117 PEs uniquely found in the brain, and 1,214 showing differential splicing in brain compared to other tissues. To identify pathogenic variants affecting PE splicing, we leveraged the ClinVar database and SpliceAI. We identified 528 pathogenic variants predicted to alter the splicing of 345 PEs. Notably, many of these variants were associated with neurodevelopmental and neurodegenerative disorders such as frontotemporal dementia, intellectual disability and epilepsy. We validated 10 of these candidates using minigene splicing assays and genome-editing technologies. Functional analyses in vitro allowed us to elucidate the role of these PEs and associated variants. Our findings underscore the critical role of PEs in the brain and lay the foundation for developing novel therapeutic strategies for incurable neurological disorders.

POSTER NUMBER:
81

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PMS1 as a potential therapeutic target for Huntington's Disease

Investigators: N. Doherty, M. Wu, M. Pires, M. Kesavan, J. Roy, V. Wheeler, R. Mouro Pinto

Huntington's Disease (HD) is a rare, devastating neurodegenerative disease with no cure, caused by a CAG repeat expansion in exon 1 of the HTT gene. Postmitotic alteration of the expanded CAG repeats, somatic repeat instability, plays an important role in HD onset and progression. Our previous investigations in HD model mice revealed significant involvement of mismatch repair (MMR) genes, including Pms1, in this instability process. Notably, PMS1 was identified as a modifier gene of clinical phenotypes of HD patients in genome-wide association studies. These findings suggest the potential of MMR genes as therapeutic targets for HD. However, given that dysfunction in some MMR genes can lead to carcinogenesis, it is crucial to identify targetable genes that do not increase malignancy risks. Low oncogenic potential of PMS1 led us to hypothesize PMS1 could be a viable therapeutic target for HD. To address this, we assessed the impact of Pms1 knock-out (KO) in Htt.Q111 model mice:

1) Somatic repeat expansions: Significantly suppressed in Pms1KO/KO animals.

2) Transcriptional dysregulation: Bulk RNA sequencing demonstrated significant rescue of dysregulated genes in the striatum of Pms1KO/KO animals at 10 months.

3) Accumulation of mutant huntingtin (mHTT) protein: Immunohistochemistry in striatal sections revealed significant suppression of mHTT accumulation in Pms1KO/KO animals at 10 months.

Overall, our results demonstrated a significant rescue effect on the genetic and molecular phenotypes of HD model mice. Also importantly, the Pms1KO/KO mice exhibited no detectable tumors and presented normal lifespan. These findings suggest Pms1 as a promising therapeutic target for HD.

Health Disparity and Health Equity Research

POSTER NUMBER:
82

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The Association of Food and Housing Insecurity and Resource Placement in Boston

Investigators: J. Jaramillo, M. A. Meeker, M. Perkins, D. Taitelbaum, L. Fiechtner, R. H. Marsh, L. Simon, M. Samuels-Kalow, EMNet

Community resources are vital to addressing adverse social determinants of health, especially from the emergency department. Our goal was to examine the availability of emergency food and housing resources in relation to community need to identify areas of mismatched resources and insecurity.

A cross-sectional study was conducted combining data from the Massachusetts Annual Statewide Survey on Food Insecurity, Equity & Access (2022), the American Community Survey (2022), and a Boston area food and housing resource index (2024). Spatial clustering was measured using Moran's I. A descriptive analysis summarized the association between median income and resource/insecurity discordance across census tracts. Discordance was defined as either under-resourced, where there was no relevant resource in a census tract with high insecurity, or over-resourced, where there was at least one relevant resource in a tract with low insecurity.

There was significant spatial clustering of food insecurity, housing insecurity, and housing resources ($p<0.001$). For census tracts with a median household income below 200% of the federal poverty line ("experiencing poverty"), 40% (38) were under-resourced for housing and 50% (48) had no immediate food resources. Comparatively, for census tracts not experiencing poverty, 17% (70) were under-resourced for housing and 10% (44) had no immediate food resources.

Our findings indicate that while food and housing insecure areas were clustered, related resources were not in these areas of need, and census tracts experiencing poverty had higher rates of unmet needs. Our findings also emphasize that emergency-based social referral programs may struggle to identify appropriate resources in high-needs areas.

POSTER NUMBER:
83

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Leveraging a Quality & Safety Continuous Process Improvement Framework to Address Disparities in Breast Cancer Screening

Investigators: P. Dhar, H. Johnston, O. Piyankh, D. Jessup, E. Balasalle, Z. Sodickson, J. Lu, T. Goodman, E. Kistler, M. Paulo, D. Irizarry, G. Camareno-Soto, N. Amornsiripanitch, E. Flores

Background: Disparities in breast cancer affect underserved populations. Screening mammography (SM) can reduce these disparities through early detection. However, a high SM cancellation rate (35%) was seen in two MGB community health centers serving Hispanic/Latino women. Using a Quality & Safety continuous process improvement (QS-CPI) framework can reduce SM cancellations at these sites.

Methods: We used process mapping, driver diagrams, and Pareto charts with radiology partners and patients to identify factors for SM cancellations and develop multilevel interventions. Plan, Study, Do, Act (PDSA) cycles with continuous data monitoring refined interventions, including a multimedia text reminder (SMS) program, rideshare transportation assistance, and educational videos. These interventions were implemented over 15 months (July 2023-October 2024). We collected data on patient demographics, SM appointment metrics, rideshare usage, and video views. Statistical analyses assessed differences in SM cancellation rates post-intervention.

Results: SM appointments (n=5523) were scheduled post-SMS intervention, 73.1% (4038/5523) were completed. The cancellation rate post-intervention is 26.9% vs 29.2% pre-intervention. Patients who did not engage with SMS had a 40.4% cancellation rate versus 21.7% for those who did. Secondary outcomes showed 49.1% of patients who used the rideshare service were call-back patients for BIRADS 0. Patients (n=1158) received the educational video, 17% (n=199) watched the video. Of those, 88% completed the appointment (v.76% if they did not watch).

Conclusion: Multilevel intervention designed through a QS-CPI lowers SM cancellation rate among those who confirmed their appointment via SMS. This framework allows for scalable interventions that enhance patient-centred care, increase capacity, and reduce administrative tasks.

Health Disparity and Health Equity Research

POSTER NUMBER:
84

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Rates of retention among underrepresented minoritized groups in Alzheimer's Disease research; findings from the Longitudinal Cohort at MADRC

Investigators: M. A. Galvez, B. G. Simpson, S. Das, A. Serrano Pozo, L. Ramírez Gomez

Black and Latino older adults in the USA are at a higher risk of developing dementia compared to non-Latino whites (NLW). However, recruitment and retention of participants from these underrepresented groups in research has been limited. Barriers to participation include mistrust, perceived lack of benefits, time constraints, and transportation difficulties.

This study aimed to examine retention rates among Black and Latino participants compared to NLW participants enrolled in the Massachusetts Alzheimer's Disease Research Center (MADRC) Longitudinal Cohort (LC) between November 2021 and August 2023. Additionally, we sought to identify factors influencing retention rates across different racial and ethnic groups. We conducted statistical analyses using contingency tables and Chi-squared tests, with age, sex, education, race/ethnicity, and cognitive status as independent variables.

A total of 97 participants were included in the MADRC LC, with 87 from underrepresented groups. Retention rates varied significantly across racial and ethnic groups, with Black participants showing the lowest retention at 52%, compared to 82% in Latino participants and 60% in NLW participants ($p = 0.013$). Age, sex, education, and cognitive status did not significantly influence retention rates. These findings showed encouraging retention rates for Latinos and highlight the need for increased efforts to engage Black participants in research, such as by hiring culturally competent Black clinicians and staff. Future research should compare these findings with data from other Alzheimer's Disease Research Centers (ADRCs) to better understand and address retention challenges.

POSTER NUMBER:
85

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Strategies for Academic and Leadership Advancement among Women in Emergency Medicine

Investigators: D. James, M. Samuels-Kalow

Only 38% of United States Emergency Medicine (EM) faculty are women; an even smaller portion, 14%, are in leadership positions as Chairs. Lack of women in EM leadership roles potentially reduces diversity in decision-making, creates gender disparities in research priorities, slows progress in addressing women's health issues, and worsens structural biases hindering career advancement. However, there is limited data about how to improve academic advancement for women in EM. Our goal was to identify best practices for the academic and leadership advancement of women in EM using in-depth interviews among women faculty members. Interview questions were developed based on a literature review of 55 studies from 1992 through 2024 identifying key themes including: mentorship, training programs, grant support, recognition, institutional policies, and disparities. Based on these evidence-based findings and key priorities, semi-structured interviews were conducted among women faculty (N=17) inside/outside MGB and trained research staff to gain further insight. Completed interviews (1:1; via Zoom; ~30 minutes) were then transcribed, coded, and analyzed. Preliminary data identified five primary codes relevant to the advancement of academic and leadership roles for women in EM: 1) the importance of internal/external programs and trainings; 2) barriers to program/training engagement (e.g. lack of awareness); 3) facilitators to program/training engagement (e.g. department support); 4) the importance of rank-based, sustained mentorship; and 5) critical individual (e.g., family) and departmental structural (e.g., policies, procedures) components. Future work should integrate these findings to address and support stepwise, solution-based programs to advance academic and leadership roles for women in EM.

Health Disparity and Health Equity Research

POSTER NUMBER:
86

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Evaluating differential referrals occurring in the Tourette Syndrome Center of Excellence Clinic, Mass General Brigham: A cross-sectional study

Investigators: P. C. Lazatin, C. M. Yuen, H. Gilbert, N. Sharma, M. D. Hollins

Background: Racial disparities have been reported in recent literature identifying that racial minorities are less likely to receive a formal diagnosis of Tourette Syndrome. Early diagnosis and intervention have been proven to reduce the burden of symptoms. The study aimed to elucidate the implementation barriers to engagement of care faced by racial minorities at the Pediatric Movement Disorders Clinic at Massachusetts General Hospital.

Methodology: The care cascade was reviewed cross-sectionally. Descriptive statistics was used to quantify the proportion of patients who complete each stage. Logistic regression was used to assess the association of race with identified barriers. Potential interaction with other social determinants of health was controlled through step-wise selection, multivariable logistic, and cox-proportional hazards regression.

Results: Hispanics or non-whites are less likely to receive initial care at any specialist (OR = 0.55, p = 0.042), less likely to be formally diagnosed with TS (OR = 0.54, p = 0.006) and are subjected to longer wait times (142 days vs. 108 days, p = 0.232) compared with non-hispanic whites. Step-wise selected multivariable logistic regression showed that race is the sole significant predictor of initial care at any specialist. Final diagnosis is strongly associated with race and receiving initial care at an MGB facility. Cox-proportional hazards showed that age > 7 is significantly associated with timely engagement of care.

Conclusion: Racial disparities limit early engagement of specialist care that leads to delayed treatment of TS. Further implementation science study is needed to assess methods to reduce the implementation barriers identified.

POSTER NUMBER:
87

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Evaluating the impact of community-based dermatology education on health-seeking behaviors among persons experiencing homelessness

Investigators: C. Li, J. Nusynowitz, J. Trinidad

Homelessness in the United States remains a pressing issue, with over 650,000 persons experiencing homelessness (PEH) on a single night. Dermatologic conditions, including infections, inflammatory disorders, and skin cancers, are more prevalent among PEH. Prior studies have shown that community-based interventions can improve health-seeking behaviors. This study aimed to assess the impact of community-based dermatology education on health-seeking behaviors and skin health knowledge among PEH in Massachusetts.

A one-hour educational session covering basic skincare, sun protection, skin self-exams, and signs of skin cancer was delivered at local shelters and organizations supporting PEH in Massachusetts. Participants completed anonymous pre- and post-session surveys, rating their familiarity with dermatology, likelihood of seeing dermatology, confidence in skincare, and comfort with self-exams on 10-point Likert scales before and directly after the session.

Among 26 participants, the majority identified as Black or African American (53.8%), followed by White (30.8%), Hispanic or Latino (15.4%), and American Indian or Alaskan Native (11.5%). Participants showed improvement across all measured domains: familiarity with dermatologic conditions increased by 2.2 points (5.3 to 7.5), likelihood of seeing a dermatologist by 2.5 points (4.8 to 7.3), confidence in skincare by 2.4 points (5.9 to 8.3), and comfort with skin self-exams by 2.8 points (5.7 to 8.5).

Here, we show that community-based dermatology education can improve skin health knowledge, increase confidence in self-care, and encourage engagement with dermatologic services. The observed increases in average Likert scores across multiple domains indicate that even a brief, one-hour educational intervention can meaningfully impact health-seeking behaviors among PEH.

Health Disparity and Health Equity Research

POSTER NUMBER:
88

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Uncovering Gaps in Modeled Smoking Histories: Implications for Lung Cancer Screening Eligibility

Investigators: H. Mahmoudi, A. L. Potter, J. Di Silvestre, A. Eckel, V. Munshi, C. J. Yang, G. S. Gazelle

Purpose: Evaluate the National Cancer Institute's Smoking History Generator (SHG) for modeling smoking histories and assess its impact on lung cancer screening eligibility among racial minorities.

Methods: We analyzed data from the Southern Community Cohort Study (SCCS) and the Multiethnic Cohort (MEC) Study (70% and 80% minority, respectively), comparing SHG-generated smoking histories with real-world patterns. Discrepancies were assessed using smoking duration, pack-years, and proportions meeting established and proposed screening guidelines.

Results: Significant deviations were observed between SHG-simulated smoking histories and real-world data for the White and Black subpopulations. A markedly higher proportion of Black smokers reported fewer than 20 pack-years compared to SHG simulations, while the White subpopulation showed a much smaller proportion reporting fewer than 20 pack-years than indicated by SHG. Consequently, reliance on SHG overestimates screening benefits for Black subpopulations under current eligibility criteria and underestimates them for White subpopulations. SHG also consistently underestimates eligibility based on smoking duration thresholds, undervaluing the shift from pack-year to duration thresholds, even though duration-based criteria enhance screening for all subpopulations.

Conclusion: Here we show that relying on SHG's unstratified, pack-year–based simulation perpetuates screening inequities. Incorporating racially stratified data into SHG and related models is crucial for developing more equitable screening policies and improving health outcomes across diverse populations.

Keywords: Lung Cancer Screening, Smoking History Generator, Health Disparities

Health Disparity and Health Equity Research

POSTER NUMBER:
89

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Results From a Qualitative Study of Race and Ethnicity Data Collection in the Emergency Department

Investigators: M. Swanton, K. Ravenelle, K. Zachrison, M. Samuels-Kalow, R. Salhi, EMNet

Patient registration in the emergency department (ED) is a critical source of demographic data collection, an important first step towards high quality and equitable care. Despite the importance and widespread utilization of this data, there is minimal research on how it is collected. We sought to understand the barriers and facilitators of the collection of race and ethnicity data in the ED.

Semi-structured interviews were conducted with registrars across five hospitals within the same health system. E-mail and paper advertisements were used for recruitment. Using a purposive sampling approach, interviews were conducted via video conferencing software, recorded and transcribed. Interview questions addressed registrars' experiences collecting demographic information and elicited suggested improvements. The interviews were coded and analyzed using a hybrid content analysis and thematic analysis approach.

We conducted fourteen interviews before reaching thematic saturation. Five themes were identified: (1) Inconsistencies in training (2) Knowledge around the utilization of demographic data, (3) Challenges posed by the ED environment (including insufficient private spaces, lack of space for registration staff, and patient characteristics), (4) Communication decisions (when to ask), and (5) Question strategies (how to ask). Understanding the use of demographic data was identified as a facilitator for registrars to feel comfortable asking about race and ethnicity. Suggested interventions included longitudinal, consistent training sessions and in-person practice.

The ED environment and staff members' understanding of the goals of data collection influence if and how they ask demographic questions. Future interventions should center on the identified themes to improve data collection in the ED.

Health Disparity and Health Equity Research

POSTER NUMBER:
90

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The Role of Transnational Families and the Asylum Process among U.S. Asylum Seekers

Investigators: M. Nimblette, S. S. Fauza, M. S. Velasco, A. S. Saadi

Introduction: Asylum seekers in the U.S. experience unique challenges within family units. Familial relationships can buffer migration-related stress or deteriorate after migration due to severed ties and distance, influencing health behaviors, outcomes, and overall wellbeing. Less is known about the experience of U.S. asylum seekers. Our study explored how familial relationships evolve during the U.S. asylum adjudication process.

Methods: Longitudinal interviews approximately 3 months apart took place between August 2022 and October 2023 and were analyzed using a hybrid inductive-deductive thematic approach (n=18 at T1, n=14 at T2).

Results: Analysis revealed four themes: 1) Challenges of family separation, with straining or severing of social ties due to extended periods of separation, stress from financial burdens, guilt of leaving family behind (including children), and decreased transparency with family abroad about the asylum process; 2) Development of transnational family identity, including navigating acculturative stress, parent-child conflict, evolving concepts of intimacy, and family across borders; 3) Technology as both facilitator and barrier to maintaining family bonds, and 4) Coping mechanisms, predominantly a) Faith and religion, b) Social networks, and c) Motivation by role as a provider parent or family member.

Conclusion: Challenges of the asylum process extend to the household as asylum applicants navigate the loss of familial relationships or form new familial identities across borders. This impact highlights the need for increased support from health professionals to address family-related challenges.

POSTER NUMBER:
91

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Geospatial Analysis of Penicillin Allergy De-Labeling

Investigators: K. G. Blumenthal, A. J. King, V. E. Stone, S. Bartels, D. T. Norton, M. L. Eippert, Y. Zhang, A. Wurcel

Penicillin allergy labels are commonly placed in childhood after low-risk reactions despite no true allergy. Prescription of alternative antibiotics leads to inferior outcomes, increased antimicrobial resistance (AMR), and adverse effects. Removing a penicillin allergy mislabel from a patient's record, "de-labeling," is an evidence-based strategy that permits beta-lactam antibiotic prescribing. We assessed how geospatial socioeconomic indicators relate to penicillin allergy de-labeling prevalence.

Electronic health record data identified primary care patients at Mass General Brigham and Tufts Medicine with a penicillin allergy record. Using a validated algorithm, we determined de-label status then assessed de-labeling prevalence across greater Boston, comparing high versus low per capita income. We merged patient zip codes to geospatial data to calculate validated indicators: the Social Vulnerability Index (SVI) and American Community Survey uninsured and unemployment rates. We assessed penicillin allergy de-labeling prevalences across each indicator's quartiles and estimated prevalence ratios (PR) with 95% CI. Adjusted PRs control for patient age, sex, race, ethnicity, and hospital system. The de-labeling prevalence was on average 6.4% higher in the highest income areas compared to the lowest (p=0.004). SVI demonstrated lower de-labeling prevalence in areas more socially vulnerable and lower socioeconomic status. De-labeling prevalence was also lower in areas with higher uninsured and unemployed rates (p for trends<0.001). These data suggest inequitable access or uptake of penicillin allergy de-labeling across socioeconomic differences, despite similar demographics and primary care institutions. Given disparities in antibiotic prescribing and AMR infections, improving equitable access to penicillin allergy de-labeling is key to improving infectious diseases outcomes.

POSTER NUMBER:
92

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Assessing the influence of socioeconomic factors on transgender patients with hidradenitis suppurativa

Investigators: J. Nusynowitz, N. Gessner, C. Li, A. Patel, D. Ozisik, N. Shah, M. DeWane, J. C. Trinidad

Hidradenitis suppurativa (HS) is a chronic inflammatory disease affecting hair follicles, with sex hormones implicated in its pathogenesis. Transgender and gender-diverse (TGD) individuals on gender-affirming hormone therapy (GAHT) may face increased HS risk. Both HS and TGD populations encounter significant healthcare barriers, yet the interplay between HS, TGD health, and socioeconomic factors remains poorly understood. This study examines the role of socioeconomic status (SES), including income, insurance coverage, and other sociodemographic factors, in HS severity among TGD patients.

This retrospective analysis identified adult transgender patients treated for HS from 2000 to 2024 at Mass General Brigham. Demographic (e.g., sex assigned at birth, Medicaid status), behavioral (e.g., substance use), and clinical data (e.g., age at HS diagnosis, GAHT history) were collected. Zip codes were categorized by income level: lower (<$52,000), middle ($52,000-$156,000), and upper (>$156,000). Fisher's exact and Kruskal-Wallis tests ($p<.05$) assessed associations between variables and HS severity.

Among 35 patients, 54% identified as male, 29% as female, and 14% as non-binary. Most (74%) were white, and the average age of diagnosis was 26 years. Nearly half (46%) were on Medicaid, and 71% resided in middle-income zip codes. Lower income significantly correlated with more advanced HS at diagnosis ($p<0.005$).

Here we show that socioeconomic barriers, including lower income and Medicaid enrollment, are associated with more severe HS in TGD patients. Addressing social determinants of health is critical to improving access to timely care and reducing disease burden in this vulnerable population.

Health Disparity and Health Equity Research

POSTER NUMBER:
93

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Racial and Ethnic Disparities after Hip Fracture in Older Adults with Type 2 Diabetes

Investigators: K. M. Okazaki, S. M. Burnett-Bowie, L. A. Marion, S. J. Cromer, J. Ortega-Montiel, C. F. Alix, E. Patorno, J. M. Paik, E. W. Yu

Purpose: Racial and ethnic (R&E) disparities in post-hip fracture mortality have been documented in the general population, but their impact on individuals with type 2 diabetes (T2D) is unclear. T2D is also associated with increased fracture risk and worse post-hip fracture outcomes.

Methods: Using 2015-2020 Medicare fee-for-service data, we identified adults >65 years old with T2D who sustained hip fractures. We assessed rates of post-hip fracture 365-day mortality, refracture, bone density testing, osteoporosis treatment, and incident destitution rates across R&E groups using Cox regression models adjusted for age and sex.

Results: Among 111,256 adults with T2D and hip fracture (mean age 82±8 years, 73% female), 88% were non-Hispanic White (NHW), 6% non-Hispanic Black (NHB), 3% Hispanic, 2% Asian, and 1% Native American (NA). NHB and NA individuals fractured at younger ages (11-12% aged 66-69 vs. 6-7% in other groups, p<0.001). NHB individuals had higher prevalence of microvascular diabetes complications, chronic kidney disease, frailty, and low SES (p<0.001). Overall, 365-day mortality was 32%. NHB individuals had higher mortality (HR 1.26 [1.20-1.31]), while Asian and Hispanic patients had lower mortality than NHW individuals (HR 0.78 [0.73-0.83] and 0.91 [0.86-0.96], respectively). Compared to NHW individuals, NHB individuals had lower rates of refracture (HR 0.76 [0.66-0.87]), bone density testing (HR 0.50 [0.45-0.56]), and osteoporosis treatment (HR 0.58 [0.51-0.65]), and higher incident destitution rates (HR 1.41 [1.29-1.55]).

Conclusion: Significant R&E disparities exist in post-hip fracture treatment and outcomes among T2D patients. Further research is needed to identify mediators of these disparities and improve post-fracture care.

POSTER NUMBER:
94

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Sex-based differences in clot strength among patients with peripheral artery disease receiving antiplatelet treatment

Investigators: A.A. Rodriguez Alvarez, I.F. Cieri, M. Boya, S.S. Patel, A. Dua

Sex differences in platelet aggregation among peripheral artery disease (PAD) patients are not well characterized. The study aimed to evaluate the impact of antiplatelet therapy on platelet reactivity in men versus women. This is a prospective cohort study of patients with PAD undergoing revascularization from December 2020- February 2024. Participants were stratified based on antiplatelet therapy (mono antiplatelet therapy-MAPT, or dual antiplatelet therapy-DAPT), with DAPT comprising patients on both aspirin and clopidogrel/ticagrelor. Coagulation profiles, specifically clot strength, using thromboelastography (TEG) and platelet mapping (PM) were assessed pre- and post-operatively. Descriptive statistics were applied to characterize each group, and a Mann-Whitney U test was conducted to assess differences in platelet function between sexes. A total of 239 patients met study criteria, of which 34% were women, 88% were Caucasian, and 69% were on MAPT, with a mean age of 70 years. Overall, women exhibited greater clot strength as indicated by Citrated Kaolin Maximum Amplitude (MA) [61.63mm vs. 59.94mm, p<0.05] and Citrated Rapid TEG (CRT) MA (62.76mm vs. 61.2mm, p<0.05). These findings were consistent within the MAPT group, where women exhibited a higher CRT MA (63.44mm vs. 60.79, p<0.05) and Arachidonic Acid MA (40.43 vs. 34.24 mm, p<0.05), suggesting a greater platelet hyperactivity in women. Conversely, within the DAPT group, clot strength remained consistent across both sexes. Women showed higher clot strength in the MAPT compared to males in spite of being on the same medications.

Health Disparity and Health Equity Research

POSTER NUMBER:
95

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"I'm sorry, I can't hire you because of that": Examining the role of employment and exclusion on health and well-being among U.S. Asylum Seekers

Investigators: L. Sabbah, M. Velasco, A. Saadi

Introduction/Objectives: Employment is a social determinant of health, providing differential access to health insurance, social networks, and other resources that influence health trajectories. We qualitatively assess U.S. asylum seekers' experiences at the intersections of immigration, employment, and health and well-being.

Methods: English and Spanish-speaking adult asylum seekers (age >/=18 years old) were recruited predominantly from the MGH Asylum clinic, as part of a longitudinal, mixed-methods pilot study assessing how the asylum adjudication process impacts the health of U.S. asylum seekers. The study utilized survey questionnaires and semi-structured interviews at two time points over the course of a year (n=18 at T1 and n=14 at T2).

Results: We identified six themes: 1) Employment as integral to the experience of the asylum process; 2) Obtaining a work permit during asylum adjudication as a lengthy process which resulted in limited access to necessities and health services, and people resorting to desperate methods to obtain income; 3) Underemployment, which involved suboptimal opportunities due to devaluing of experience in their home country, transportation challenges, and competing demands; 4) Workplace inequity and exploitation; 5) Employment representing opportunity for advancement and stability which included hopefulness, self-improvement, and skill building; and 6) Work as part of asylum-seekers' self-concept and desire to contribute to their new communities.

Conclusion: Our study highlights the employment challenges faced by U.S. asylum seekers, which can harm their health and well-being. Increasing pathways to employment during the asylum adjudication process can be one mechanism for promoting health and well-being in this population.

POSTER NUMBER:
96

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From Community to Commencement: Analyzing the Correlation Between Social Capital Variables And Graduation Rates Among United States High Schools

Investigators: S. A. Saldivar, D. M. Cutler

How do the strength and interconnectedness of a community influence student education outcomes within that community? In this paper, I employ two novel measures of social capital—Economic Connectedness and Social Clustering, created and detailed by Opportunity Insights—to study their relationship with graduation rates at the high school level. Economic Connectedness and Social Clustering measure the degree to which low and high socioeconomic individuals are friends with one another and the degree to which social networks are intertwined in a community, respectively. These variables are constructed using Facebook friendships from May, 2022. Controlling for well-known predictors of educational success, such as median parent income and student demographics, I run regressions between graduation rates and my two variables of interest. My results show that a one standard-deviation increase in economic connectedness is associated with a 2.46 percentage point increase in graduation rates when including controls and state fixed effects in the model. An analogous increase in social clustering is associated with a 1.13 percentage point increase in graduation rates when including the same controls and fixed effects. These increases are substantial as they represent a minimum of 7.5 percent of the gap between the national average graduation rate (87 percent) and a perfect 100 percent rate. These findings highlight the potential benefits of fostering socioeconomic diversity and stronger community ties within school districts to improve educational outcomes in the United States.

Health Disparity and Health Equity Research

POSTER NUMBER:
97

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Penicillin Allergy De-Labeling Disparities in Gender Marginalized Groups

Investigators: R. J. Shah, A. McDowell, A. King, Y. Zhang, A. G. Wurcel, K. G. Blumenthal

Background: Gender marginalized populations have an increased risk of sexually transmitted infections, many of which are optimally treated with β-lactam antibiotics that may be avoided in patients with a penicillin allergy label. Despite the importance of evaluating inaccurate penicillin allergies on antibiotic stewardship, it is unknown whether penicillin allergy de-labeling disparities exist among gender marginalized individuals. This study evaluates the association between gender identity and penicillin allergy de-labeling at a large academic health system.

Methods: We conducted a retrospective cohort study of primary care patients with a penicillin allergy label (PAL) at Mass General Brigham from 2019–2022. Patients were classified as transgender, non-binary, or cisgender based on electronic health record gender identity variables. Penicillin allergy de-labeling prevalence was compared across groups, and standardized prevalence ratios (SPRs) were calculated to adjust for group differences in age and race.

Results: Among 46,854 patients with a PAL, de-labeling prevalence was 9.5%. Transgender patients (n=79) had lower de-labeling (2.5%) compared to cisgender (n=46,641; 9.5%) and non-binary (n=134; 9.0%) individuals. After standardized prevalence by age and race for the cisgender population, transgender patients were significantly less likely to be de-labeled (SPR: 0.3; 95% CI: 0.0-0.7), while non-binary patients had a de-labeling prevalence comparable to cisgender individuals (SPR: 1.0; 95% CI: 0.4-1.5). Non-white transgender patients had no recorded penicillin allergy de-labeling.

Conclusions: Transgender individuals had a lower penicillin allergy de-labeling prevalence, which may increase the risk of broader spectrum or less effective antibiotic prescribing and adverse health outcomes.

Immunology/Inflammation

POSTER NUMBER:
98

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Neutrophil Inflammation as a Key Driver in Pediatric Post-Acute COVID-19 Syndromes

Investigators: B. S. Alvarez-Carcamo, J. Greatorex, T. J. LaSalle, F. Ellet, Z. Swank, R. McCarthy, L. Guthrie, M. B. VanElzakker, A. D. Proal, D. Walt, A. Fasano, M. Sade-Feldman, D. Irimia, L. M. Yonker, PolyBio

Background: Long COVID (LC) is a post-infectious syndrome with persistent neurological, respiratory, and cardiovascular symptoms, affecting ~8% of the population. While inflammation is recognized in LC, the neutrophil's role is understudied. We sought to define neutrophilic gene expression and function to determine its role in immune dysregulation in LC.

Methods: Whole blood was collected from pediatric participants with LC and healthy controls (HC) (IRB #2020P000955). Isolated neutrophils were loaded into microfluidic technology to study NET formation, phagocytosis, chemotaxis, and spontaneous migration. Fluorescent microscopy videos were analyzed using ImageJ. Gene expression was assessed by bulk transcriptional analysis. Clinical metadata was extracted from medical records and symptom surveys.

Results: 54 children and young adults with LC, 19 with MIS-C, and 65 HC were enrolled (mean age: 13 years; 46% female). LC neutrophils displayed increased spontaneous NETosis ($p<0.0001$) but reduced chemotaxis ($p<0.05$) and phagocytosis ($p<0.05$) compared to HC, along with significant increases in IFNγ, IL-4, and IL-5. Elevated levels of IL-1β and IL-2 were strongly associated with LC, corresponding with alterations in inflammatory gene expression profiles. Further, we found that increased exposure to Spike-immune complexes induced a dose-related response in NETosis, suggesting Spike antigenemia, in part, corresponds with neutrophil inflammation in LC and MISC.

Conclusions: LC and MIS-C exist on a continuum, sharing immunopathological features such as elevated NETosis and dysregulated cytokine release. Dose-dependent response to Spike may explain the range of the severity of neutrophil activation. Current studies are investigating whether larazotide, a zonulin inhibitor, can reduce Spike-mediated neutrophil activation in LC.

Immunology/Inflammation

POSTER NUMBER:
99

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Role of Proton-Secreting Epithelial Cells in Shaping Urogenital Tract Mucosal Immunity

Investigators: M. C. Avenatti, M. L. Elizagaray, F. Barrachina, I. Bastepe, M. A. Battistone

Acute Kidney Injury (AKI) affects one in five hospitalized adults and causes 300,000 annual deaths in the U.S. yet lacks early diagnostic tools and targeted therapies. This study investigated the cellular and molecular mechanisms underlying the communication between epithelial intercalated cells (ICs) and immunocytes under homeostatic and injury conditions. Specifically, it examined their interaction in surveying the renal epithelial barrier and regulating inflammation-tolerance balance. To disrupt renal immune tolerance, Foxp3^{+} regulatory T cells (Tregs) were depleted by injecting diphtheria toxin (DT) into male and female Foxp3-DTR mice, which express the DT receptor under the Foxp3 promoter. Two weeks after renal Treg ablation, severe autoimmune nephropathy was triggered, characterized by aggravated immune cell infiltration, renal autoantibody deposition, glomerular and tubular damage, and compromised kidney function. Specifically, flow cytometry revealed neutrophils, macrophages, and B cells invading renal tissue, alongside increased antigen-presenting cells. Elevated renal IgG, IgM, IgA, IgG1, and IgG2c autoantibodies were detected by ELISA. Confocal microscopy showed antibody deposition in the glomeruli and around the tubules, along with glomerular hypertrophy and proximal tubular injury. Functional renal impairment was demonstrated by an increase in urine albumin/creatinine ratio, reduced urine output, and elevated blood urea nitrogen/creatinine levels. RNA sequencing of ICs post-Treg depletion showed upregulation of pro-inflammatory genes driving autoimmune kidney injury. Notably, ICs upregulated Il33, an alarmin that signals tissue damage and activates tissue Tregs, revealing novel IC-Treg crosstalk. Our research reveals spatial and temporal immune-epithelial interactions in AKI, highlighting a specific subgroup where targeted intervention could prevent disease progression.

POSTER NUMBER:
100

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Investigating the Effect of Type 2 Inflammation on Dynamic Secretory Cell Antigen Passaging

Investigators: S. Zwick, E. Chen, K. Sun

The airway epithelium is constantly exposed to noxious agents, such as allergens, irritants and pathogens. To protect against these assaults, the epithelium not only acts as a secure barrier, but also samples and relays antigens to the underlying immune system. Our group recently showed the presence of secretory cell associated antigen passages (SAPs), a dynamic phenomenon in which secretory cells function as both protein secretors and antigen samplers. Airway SAPs are stimulated through acetylcholine, but other mechanisms of SAP upregulation remain unknown. It was recently demonstrated that in the intestine, analogous goblet cell associated passages (GAPs) in intestinal epithelia are stimulated by Th2 cytokine IL13. Here, we hypothesize that Th2 inflammation may upregulate SAP formation in the airway and may be clinically relevant to mechanisms relating to allergen detection. We utilize mouse trachea air-liquid interface (ALI) cultures, secretory cell lineage tracing, and sectional confocal microscopy to determine whether Th2 stimuli may upregulate SAP activity. Traditional fluorescent microscopy revealed an elevated intake of dextran antigen by ALIs stimulated with IL13; sectional confocal microscopy juxtaposing secretory lineage tracing cells with dextran-positive cells displayed overlap, suggesting increased SAP activity in IL13-administered ALIs. Furthermore, we observed a positive relationship between dextran uptake and the number of days ALIs were incubated with IL13, suggesting that IL13 upregulates SAP antigen uptake in a time-dependent manner. These results taken together imply that the Th2 immune pathway may exert influence on the dynamic antigen sampling activities in SAPs, which may increase our fundamental understanding in allergen pathology.

Immunology/Inflammation

POSTER NUMBER:
101

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Association of Distinct Microbial and Metabolic Signatures with Microscopic Colitis

Investigators: A. S. Chen, H. Kim, E. Nzabarushimana, J. Shen, K. Williams, J. Gurung, J. McGoldrick, K. E. Burke, J. C. Yarze, L. H. Nguyen, K. Staller, D. C. Chung, R. J. Xavier, H. Khalili

Microscopic colitis (MC) is a chronic inflammatory disease of the large intestine that primarily affects older adults and presents with chronic diarrhea. The etiology is unknown and there are currently no FDA approved medications or biomarkers for treatment or monitoring of the disease. Emerging evidence have implicated the gut microbiome and metabolome disturbances in MC pathogenesis. We conducted a comprehensive analysis of gut microbial and metabolic changes in a longitudinal cohort of 683 participants, including 131 patients with active MC, 159 with chronic diarrhea, and 393 age- and sex-matched controls without diarrhea. Gut microbiomes were profiled using whole-genome shotgun metagenomic sequencing, and metabolomes using ultra-high performance liquid chromatography–mass spectrometry. Compared to control, eight microbial species including pro-inflammatory oral-typical Veillonella dispar and Haemophilus parainfluenzae, and 11 species, including anti-inflammatory Blautia glucerasea and Bacteroides stercoris were enriched and depleted in MC, respectively. Pro-inflammatory metabolites, including lactosylceramides, ceramides, lysophospholipids, and lysoplasmalogens, were enriched in active MC. Multi-omics analyses revealed robust associations between microbial species, metabolic pathways, and metabolites, suggesting concordant disruptions in MC. Our findings suggest distinct shifts in gut microbiome and metabolome in MC that can inform the development of non-invasive biomarkers and novel therapeutics.

POSTER NUMBER:
102

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Enhanced placental antibody transfer efficiency with longer interval between maternal respiratory syncytial virus vaccination and birth

Investigators: O. J. Jasset, P. A. Lopez Zapana, Z. Bahadir, L. Shook, M. Dennis, E. Gilbert, Z. A. Liu, R. V. Yinger, C. Bald, C. G. Bradford, A. H. Silfen, S. J. Feinerman, J. C. Remland, O. A. Jimenez, L. Ibanez-Pintor, S. L. Klein, A. Pekosz, S. Permar, L. Konnikova, L. M. Yonker, D. Lauffenburger, A. Nelson, M. A. Elovitz, A. G. Edlow

Objective: Respiratory Syncytial Virus (RSV) is a leading cause of infant respiratory disease and hospitalization globally. In September 2023, the CDC recommended the administration of the RSV vaccine to pregnant individuals between 32+0 to 36+6 weeks of pregnancy to reduce infant morbidity and mortality from RSV. We sought to investigate how time elapsed from maternal RSV vaccination to delivery impacts placental antibody transfer to the umbilical cord at delivery.

Study design: IgG antibodies against RSV strain A2 and B fusion (F) and attachment (G) proteins and against pertussis toxin (a comparator antigen from a vaccine routinely administered earlier in pregnancy) were quantified using a Binding Antibody Multiplex Assay in the maternal and/or cord blood of 124 individuals who received the RSV vaccine in pregnancy (enrolled September 2023 - March 2024). Differences in cord:maternal transfer ratios by timing of maternal vaccination were evaluated by Kruskal-Wallis tests.

Results: Maternal vaccination 2-3 weeks and 3-4 weeks prior to delivery was associated with significantly lower cord:maternal transfer ratios than those observed when vaccination occurred >5 weeks prior to delivery (P=.03, P =.007; respectively), and transfer ratios were significantly lower than those observed for pertussis vaccination administered prior to 30 weeks of gestation (P =.008, P =.03; respectively).

Conclusion: Vaccine administration earlier in the approved 32-36 week window (≥ 5 weeks before delivery) allows for the most efficient antibody transfer. These results suggest that clinical guidance for vaccination timing within the approved window may need to be refined to optimize neonatal protection.

Immunology/Inflammation

POSTER NUMBER:
103

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Lipid metabolic pathways linked to STING signaling and interferon-B gene induction in macrophages and dendritic cells

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STING, an endoplasmic reticulum (ER)-resident signaling adaptor, plays a central role in the innate immune response to cytoplasmic DNA of microbial and endogenous origin. Upon binding to 2'3'-cyclic GMP-AMP produced by the DNA sensor cGAS, STING undergoes a series of molecular events leading to its activation—conformational changes, higher-order oligomerization, ER-to-Golgi translocation, and palmitoylation. Activated STING mediates phosphorylation of the transcription factor IRF3 by the protein kinase TBK1, prompting IRF3-driven interferon (IFN) gene transcription. STING signaling, when timely and held in check, contributes to immune defense against microbial pathogens and cancer. Unrestrained STING activation, however, causes immunopathology, as seen in various genetic disorders and chronic diseases. We postulated an interplay between STING signaling and lipid metabolism, given that STING activation is guided by dynamic molecular partitioning in membrane compartments, long-chain fatty acid modification, and other processes controlled by cellular lipid availability. To explore this possibility, we screened small-molecule compounds targeting lipid metabolic pathways for their influence on mouse and human STING signaling. These screens identified inhibitors of the fatty acid synthase FAS and the cytoplasmic lipase LIPE as potent suppressors of STING agonist-responsive phosphorylation events and IFN induction. An inhibitor of SOAT1, a key enzyme for cholesterol esterification, exerted divergent effects, enhancing IFN induction in mouse cells and attenuating it in human cells. All of these inhibitors perturbed molecular events downstream of STING without altering its palmitoylation. These findings reveal novel mechanisms linking STING signaling to lipid metabolism and new opportunities for treating conditions arising from aberrant STING activity.

Immunology/Inflammation

POSTER NUMBER:
104

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Somatic variant predictors of cutaneous immune-related adverse events in cancer patients treated with immunotherapy

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Cutaneous immune-related adverse events (cirAEs) affect nearly one-third of patients treated with immune checkpoint inhibitors (ICIs). Whether tumor somatic mutations are associated with the risk of cirAE development remains unknown.

We analyzed tumor somatic single nucleotide variants (SNVs) in 733 patients with stage III/IV melanoma receiving ICIs at Dana Farber Cancer Institute and Massachusetts General Hospital. Nonsynonymous SNVs were used to calculate tumor mutational burden (TMB) and determine gene mutation status. Logistic and cox regression models were used to test the association between gene mutation status and the binary outcome cirAE and cirAE development, respectively. Models were adjusted for demographic and clinical covariates. Findings were validated in an independent cohort of 792 non-melanoma ICI-treated patients.

While high TMB (>10 mutations/Mb) was significantly associated with improved overall survival (HR = 0.72 [0.53, 0.98]) in melanoma, it was not associated with cirAE development (HR = 0.92 [0.69, 1.22]). Logistic regression revealed somatic mutations in PRKCI (OR = 2.76 [1.27, 6.33]), STAG2 (OR = 2.25 [1.09, 4.80]), and CXCR4 (OR = 2.56 [1.02, 6.80]) increased cirAE odds. Time-to-event analyses identified these mutations and five additional genes (MEN1, AKT3, FANCG, DAXX, H3F3B) were associated with increased risk of cirAE development (nominal p-values<.05). In the validation cohort, CXCR4 mutations were significantly associated with time to cirAE (HR = 4.02 [1.22, 13.21]). CXCR4 mutations in cirAE patients (33%) localized to the C-terminus were predicted deleterious, and altered key residues involved in CXCR4 degradation, suggesting a mechanistic link between CXCR4 gain-of-function mutations and increased risk of cirAE.

Immunology/Inflammation

POSTER NUMBER:
105

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Defensive tolerance drives the reprogramming and dysfunction of infiltrating pathogenic B cells resulting in the promotion of tolerance

Investigators: K. Hayashi, T. Yokose, J. Lancey, E. Szuter, B. Kwon, F. Murillo, I. Rosales, G. Cosimi, M. T. Guinn, P. T. Sage, P. S. Russell, A. Cosimi, J. C. Madsen, R. B. Colvin, A. Alessandrini

Background: Kidney allografts transplanted across certain mouse strain combinations are spontaneously accepted through natural tolerance. Single-cell RNA sequencing (scRNA-seq) previously revealed a transition in kidney allograft from T-cell dominance to a B-cell-rich population with an increased regulatory B-cell (Breg) signature by six months post-transplantation. However, the functional role of B cells in our tolerance model remains unclear.

Methods: Using scRNA-seq, we examined the dynamics of B-cell clusters in accepted and rejected grafts from one week to six months post-transplantation. To investigate the role of B cells in natural tolerance, we analyzed kidney graft acceptance in μMT mice (which lack B cells) and B-cell-depletion models. Additionally, kidney transplants were performed in gene-knockout recipients to evaluate the impact of genes identified by scRNA-seq, such as Fcgr2b.

Results: Despite increased Breg signatures in accepted kidney allografts, Bregs were not essential for the induction and maintenance of tolerance, as μMT mice and B-cell-depletion models accepted grafts. scRNA-seq revealed time-dependent intragraft upregulation of Fcgr2b, encoding FcγRIIB, a negative B-cell regulator. Trajectory analysis showed naive B-cell reprogramming into Fcgr2b-expressing clusters. FcγRIIB-knockout recipients resulted in rejection (mean survival: 21 days) with acute and chronic antibody-mediated rejection features and donor-specific antibodies in serum.

Conclusions: We show that FcγRIIB in B cells is crucial for kidney allograft tolerance. FcγRIIB deficiency disrupts tolerance, leading to antibody-mediated rejection. These findings highlight the importance of reprogramming infiltrating pathogenic B cells into FcγRIIB-expressing clusters for maintaining tolerance through a process we term “defensive tolerance.” This novel pathway protects kidney allografts from rejection.

Immunology/Inflammation

POSTER NUMBER:
106

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Sex differences in cord blood inflammation at birth in offspring exposed to gestational diabetes mellitus

Investigators: L. Ibanez-Pintor, S. Torres-Bigio, C. Ichugu, D. Han, P. Upadhyay, C. Powe, M. F. Hivert, A. Edlow, L. Shook

Objective: Exposure to gestational diabetes mellitus (GDM) in utero impacts the cardiometabolic health and neurodevelopment of offspring, with different risks for boys and girls. Sex-specific programming mechanisms represent a significant knowledge gap. IGFBP1 is a biomarker of insulin sensitivity in pregnancy and downregulates pro-inflammatory pathways. We have shown that in GDM, placental expression of IGFBP1 is reduced in pregnancies with a male fetus but increased in those with a female fetus. We tested the hypothesis that cord blood inflammatory factors are increased in males exposed to GDM in utero but decreased in females. Study Design: 40 pregnant individuals with live singleton term births enrolled in the MGH pregnancy biorepository (08/2020 – 02/2024) were included: 20 with GDM (N=10 females, 10 males) and 20 without GDM (N=10 females, 10 males). Analytes were quantified in umbilical cord plasma at delivery using a 20-Plex bead-based immunoassay (ThermoFisher). The impact of fetal sex and GDM on cord plasma analyte concentrations was assessed by two-way ANOVA. Spearman correlations were calculated between placental IGFBP1 expression and cord plasma analytes.

Results: Placental IGFBP1 is inversely correlated with cord plasma TNF-α (p=0.046). CCL3 levels are sexually dimorphic: higher in GDM-exposed males and lower in females (GDM-sex interaction p=0.007); CCL4 showed a similar trend (p=0.088). IFN-α, IL-6, and IL-17A levels are elevated in males (p=0.029, p=0.007, p=0.047) independent of GDM. Conclusions: In GDM, cord plasma chemokines expressed by activated monocytes are sexually dimorphic and may relate to proinflammatory pathways in the placenta, suggesting sex-specific mechanisms of offspring developmental programming.

Immunology/Inflammation

POSTER NUMBER:
107

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Fgl2 is an immunomodulatory molecule that is upregulated in tolerant kidney graft recipients

Investigators: J. L. Lancey, K. Hayashi, E. S. Szuter, T. Yokose, P. S. Russell, R. B. Colvin, A. B. Cosimi, J. C. Madsen, A. Alessandrini

Mouse kidney allografts are spontaneously accepted in select, fully mismatched donor-recipient strain combinations (i.e., DBA/2 to B6) without any immunosuppressive treatment through natural tolerance. We have previously shown using scRNAseq data that Fgl2 is highly expressed at 3 weeks post-transplantation in infiltrating CD8+ T cells; this correlates with their transition from cytotoxic cells, into ones with regulatory-like attributes through a process we call defensive tolerance. Fgl2 encodes for Fibrinogen-like protein 2 (Fgl2), which is an immunomodulatory molecule secreted by regulatory CD8+ T cells and is induced by IFN-g.

We analyzed Fgl2 expression patterns from scRNAseq data from total cells isolated from kidney grafts 3 weeks post-transplant. QuantiGene Plex (QCP) Analysis was used to assess IFN-g -dependent Fgl2 expression within WT and IFN-g KO recipients, and an ELISA was performed to measure circulating Fgl2 protein levels in accepted kidney graft recipients.

We found that Fgl2 was expressed in donor renal stromal cells and demonstrated that Fgl2 expression on intra-graft T cells is dependent on IFN-g. ELISA assays also revealed that greater levels of Fgl2 were detected in the sera of recipients with a tolerated graft when compared to sera from naïve mice.

Here we showed that the immunomodulatory molecule, Fgl2, is expressed by recipient CD8 T cells and donor stromal cells, and its expression is dependent on local IFN-g. Furthermore, Fgl2 is found in greater levels in the sera of recipients that have accepted a kidney graft. These findings suggest that Fgl2 may be crucial in understanding the immunomodulation of graft tolerance.

Immunology/Inflammation

POSTER NUMBER:
108

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Single-cell atlas of human liver and blood immune cells across fatty liver disease stages reveals distinct signatures linked to liver dysfunction and fibrogenesis

Investigators: O. P. Martin, M. S. Wallace, H. B. Patel, C. Oetheimer, M. D. Butler, J. Elbaz, C. Costentin, S. Shalloum, Z. Reinus, A. Obinelo, L. P. Wong, U. Kim, S. Shroff, K. E. Corey, E. D. Charles, R. I. Sadreyev, R. T. Chung, N. Alatrakchi, MGH Fatty Liver Clinic

Metabolic-associated steatotic liver disease (MASLD) and metabolic-associated steatohepatitis (MASH) are increasingly prevalent causes of chronic liver disease worldwide, with limited therapeutic options and an urgent need for better diagnostic biomarkers. Although immune cells regulate liver inflammation and scarring, their specific contributions to MASH progression remain unclear.

Here, we show that single-cell transcriptomics of paired liver fine-needle aspirates and peripheral blood from 25 patients spanning the MASLD/MASH spectrum uncovers distinct immune signatures underlying MASH progression. Our dual-compartment analysis identified both shared and compartment-specific cell populations whose changes parallel liver dysfunction and fibrogenesis. In terms of cell proportions, there was a significant reduction in liver-resident natural killer cells with beginning fibrosis. Some T helper cell subsets (including Th17), significantly increased in both compartments with liver fibrosis, while a subset of cytotoxic effector memory cells (CD8+GZMK+) increased only in the liver. In terms of function, analysis of gene co-expression within each cell type also revealed changes with disease. Notably, while expression of cytotoxic T-cell functions increased with inflammation in the liver, where they were considerably enriched, they surprisingly significantly decreased with fibrosis. Furthermore, examining communication signals between immune cell types revealed increasing expression of interferons and interferon-stimulated genes with disease progression.

These findings offer new insights into the immune signatures of liver pathology in MASLD/MASH and highlight the value of single-cell approaches for elucidating complex disease mechanisms. Our results lay the groundwork for future studies to validate these immune signatures as biomarkers and therapeutic targets, potentially leading to more effective clinical interventions.

Immunology/Inflammation

POSTER NUMBER:
109

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A paradox of foreign-reactive regulatory T cells and a proposed resolution by a lymph node microdomain theory

Investigators: T. Milo, S. Reich-Zeliger, N. Yosef, U. Alon, H. S. Wong

Regulatory T cells (Tregs) typically respond more strongly to self antigens than conventional T cells (Tconvs), effectively preventing autoimmune T cell responses. However, Treg reactivities to foreign antigens are much less understood. While it is known that Tregs can respond to foreign antigens, how their responses compare to Tconvs remains unclear. Based on former observations that thymic positive selection promotes T cell foreign sensitivity, we predict that Tregs may respond even more strongly to foreign antigens than Tconvs. This raises a fundamental paradox: if Tregs react more strongly to foreign antigens, how can Tconvs overcome Treg suppression and mount a robust immune response to pathogens?

To test the potential paradox, we measured self- and foreign-reactivity distributions of polyclonal Tconvs and Tregs harvested from Nur77-GFP/Foxp3-RFP reporter mice. Our preliminary data confirm that Tregs have higher self-reactivities than Tconvs. Strikingly, the data also show higher reactivities of Tregs to foreign antigens than Tconvs. Given this finding, a well-mixed lymph node structure where Tconvs and Tregs globally compete would predict that Tregs always win, making pathogen responses impossible. To settle the apparent paradox, we propose that segregation of the lymph node into many microdomains of locally competing small groups of T cells breaks the mean affinity advantage of Tregs. This spatial structure allows several high-responsive Tconv clones to overcome local Treg suppression and seed the effector response. We thus suggest that Tregs optimize immune responses by enforcing “quality control” that selects for the best responsive Tconv clones.

Immunology/Inflammation

POSTER NUMBER:
110

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RSV Immunoprophylaxis in Infants and Breakthrough Infection: Clinical Impact and Viral Features

Investigators: S. Monares, F. Taliaferro, J. Devlin, G. Adams, J. Lemieux, W. Gonzalez, L. Yonker

Background: Respiratory Syncytial Virus (RSV) is a leading cause of severe respiratory infections in infants. While new immunoprophylactic strategies (maternal vaccination [Abrysvo] and infant monoclonal treatment [nirsevimab]) mitigate disease burden in young infants, viral characteristics of breakthrough RSV infection have not been described

Methods: Nasopharyngeal swabs were collected from RSV-infected children ages <2.0 years presenting for medical care across MGH outpatient, emergency, and inpatient units between 9/2024-2/2025. RSV viral pcr cycle thresholds, genome sequences, and neutralization capacity, plus clinical outcomes, were assessed. Viral characteristics of infants immunized between 8/2024-2/2025 were compared to those with no immunoprophylaxis or remote immunoprophylaxis administered prior to 4/2024. Analysis was completed by ANOVA and Fisher's exact test.

Results: We collected 216 RSV samples; 10 (5%) were from infants with current RSV immunoprophylaxis presented for medical attention, while 206 (95%) were from infants with remote or absent immunoprophylaxis. Infants with RSV immunoprophylaxis had higher Ct values than infants with remote immunoprophylaxis ($p = 0.01$) or no immunoprophylaxis ($p = 0.3$). Three infants with current RSV immunoprophylaxis were hospitalized, compared to 26 with remote/absent immunoprophylaxis. Wheezing and antibiotic use were reported at higher rates in infants without RSV immunoprophylaxis. Viral genome analysis and neutralization assays are underway.

Conclusion: RSV immunoprophylaxis reduces disease severity, viral burden, and need for antibiotics at time of RSV infection. Analyses are underway to further characterize viral traits in breakthrough RSV infection. These data support clinical benefit in offering RSV immunoprophylaxis in pregnant mothers or to infants born during the RSV season.

Immunology/Inflammation

POSTER NUMBER:
111

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Impact of Semaglutide Use in Obese and Diabetic Patients with Hidradenitis Suppurativa

Investigators: M. I. Posada Posada, M. B. Alora, X. T. Vasconcelos Lima

Hidradenitis suppurativa (HS) is a chronic debilitating inflammatory skin disease with a complex pathogenesis. A higher prevalence of obesity in patients with HS, ranging from 5.9% to 73.1% has been noted. Semaglutide, a glucagon-like peptide-1 (GLP-1) receptor agonist, is one of the FDA-approved treatments for obesity and diabetes. Besides benefits of weight and glucose levels management, it has anti-inflammatory properties that may impact other comorbidities, such as HS.

A total of 45 patients were included: 36 females and 9 males, mean age was 42 years old and 21 were diabetic. Most patients were Caucasian and had Hurley II stage. Semaglutide starting dose was 0.52± 0.47 mg/week and increased to 1.11 ± 0.82mg/week, and 1.36 ± 0.86 respectively, at 6 and 12 months, respectively. Most patients experienced weight loss on semaglutide at 6 (5.9 ± 13.6 lb) and 12 months (10.1 ± 15.4 lb). HS improved in 27 patients after semaglutide.

There was a higher proportion of men and smokers among patients who improved on semaglutide. Higher semaglutide doses were associated with improvement at 3, 6 and 12 months. In a logistic regression model including male (OR 7.39, 95%CI 0.68-79.86, p=0.10), current smoking (OR 5.22, 95%CI 0.83-32.81, p=0.08) and 6-month dose (OR 2.76, 95%CI 1.02-7.48, p=0.045) as potential predictors, improvement remained significantly associated with semaglutide dose.

There is limited research on semaglutide in HS patients. Our findings suggest that patients taking higher semaglutide doses at any point during treatment, regardless of the presence of diabetes, showed greater improvement.

Immunology/Inflammation

POSTER NUMBER:
112

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Perturbed Gut Viral Ecology in Inflammatory Bowel Disease: A Multi-cohort Study

Investigators: J. Shen, E. Nzabarushimana, H. Kim, J. Jensen, W. Nickols, D. R. Sikavi, E. Sang, L. Chung, P. Okeagu, N. Shirai, E. A. Franzosa, C. Huttenhower, A. T. Chan, K. N. Thompson, L. H. Nguyen

Inflammatory bowel disease (IBD) is increasing worldwide, yet its viral ecology remains poorly understood. While gut dysbiosis has been linked to IBD and its subtypes, Crohn's disease (CD) and ulcerative colitis (UC), most research has focused on bacteria. We leverage a next-generation viral profiling method to analyze 2,574 metagenomes from 580 individuals across eight international cohorts.

We detected 5,391 unique viral genome bins (VGBs), the majority representing uncharacterized viral "dark matter." Notably, 78% were completely unclassified. This represents an overrepresentation of novel viruses in IBD guts compared to the 7% unclassified background in reference databases. The gut virome was 1.5x more associated with disease status than bacteria, and viral-bacterial profiles were significantly coupled. However, this coupling appeared disrupted in CD and UC. Viral and bacterial diversity decreased progressively from non-IBD to UC to CD. We further identified 343 differentially abundant VGBs in IBD, 69% more than differentially abundant bacteria. Of these viruses, 75% were uncharacterized, indicating that these novel viruses may be a critical yet underexplored factor in IBD. Among known viruses, several that were enriched in IBD are putative phages of the IBD-associated bacterium, Escherichia coli, including Punavirus P1 and Peduovirus P2. Between CD and UC, Felixounavirus felixO1 and Fohxhuevirus gastrointestinalis were differentially abundant. Finally, viral features classified IBD with accuracy comparable to bacteria in machine learning (AUC > 0.95).

Our study represents the largest virally-targeted investigation of the IBD gut to-date. Next, we will include understudied RNA viruses and interrogate the interplay between microbial domains.

Immunology/Inflammation

POSTER NUMBER:
113

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Defining Disease-Specific Epithelial Cell Phenotypes in Thyroid Autoimmunity

Investigators: E. Biederstedt, E. E. Rodriguez, V. Digania, E. Koelliker, S. Parangi, M. Rengarajan

The thyroid gland offers an ideal model to study tissue-specific autoimmunity directly in humans. The thyroid is susceptible to autoimmune attack by both cellular and humoral immunity, exemplified by Hashimoto's thyroiditis and Graves Disease, respectively. These two diseases are characterized by markedly different clinical presentations and antigenic triggers, but we and others have found that both are characterized by the emergence of a population of thyrocytes that ectopically express major histocompatibility complex class II (MHCII). MHCII is normally expressed by antigen-presenting cells, such as B cells and myeloid cells, and is not expressed in thyrocytes at baseline. In previously presented work from our lab, we found that MHCIIpos thyrocytes express genes suggestive of immune-modulation.

Here we aim to better characterize MHCIIpos thyrocytes to understand how they may modulate their local thyroid environment during autoimmune disease. We have developed an approach to selectively isolate MHCIIpos and MHCIIneg thyrocytes from surgical thyroid specimens from patients with Hashimoto's thyroiditis (n = 3) or Graves disease (n=3). We performed bulk RNA sequencing on these samples and confirmed upregulation of multiple components of the MHCII apparatus in MHCIIpos but not MHCIIneg thyrocytes. Strikingly, MHCIIpos cells exhibited a substantially different transcriptional phenotype, including up-regulation of complement factors and other immune-modulatory genes.

We have additionally developed methods to isolate specific pathogenic T-cell populations in the thyroid that our lab previously identified. We are currently examining whether MHCIIpos phenotype is associated with changes in pathogenic T-cell state in the thyroid in Hashimoto's thyroiditis and Graves disease.

POSTER NUMBER:
114

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Multiple subsets of T helper 2 lung-resident memory cells are established in a mouse model of allergic inflammation

Investigators: A. E. Taliento, W. Wang, Y. Bai, P. Lerou, J. Moon, R. Rahimi, X. Ai

Asthma is one of the most common chronic respiratory diseases. Clinical studies have shown that asthma represents a spectrum of inflammatory phenotypes, including predominantly eosinophilic, mixed eosinophilic/neutrophilic, and paucigranulocytic signatures. To investigate the mechanism underlying the heterogeneity of inflammatory phenotypes in asthma, we employed a well-established house dust mite allergen model in mice and performed Il13-Cre-mediated lineage-tracing of allergen-specific, T helper 2 tissue resident memory cells (Th2-TRMs) in the lung. Of note, allergen-specific Th2-TRMs are a central mediator of anamnestic inflammation in asthma. Single cell RNA sequencing (scRNAseq) of lineage-labelled Th2-TRMs identified a major TRM2 subpopulation (Gata3+ only) and additional subpopulations that co-expressed specific markers of Th1 (TRM2+1), Th17 (TRM2+17), and Treg (TRM2+reg) lineages, which reveals significant heterogeneity of allergen-specific, Th2-TRMs in the lung. We showed that these mixed Th lineages were generated in the acute phase of inflammation following HDM exposure and subsequently established as Th2-TRMs in the lung over time. Follow-up experiments are investigating how the heterogeneity of Th2-TRMs is regulated and whether different subpopulations play distinct roles in eosinophilic and neutrophilic inflammation upon HDM rechallenges. Our ultimate goal is to identify novel mechanisms underlying the spectrum of inflammatory phenotypes in asthma so that effective therapeutics targeting each asthma endotype can be developed.

Infectious Disease

POSTER NUMBER:
115

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The Role of Gut Microbiota on Cardiovascular Disease Progression for People with HIV

Investigators: S. Ahn, J. Huang, J. Xu, J. Elsherbini, D.S. Kwon

Human immunodeficiency virus (HIV) infection is a global health burden with approximately 39.9 million people with HIV (PWH) worldwide in 2023. With no cure for HIV, lifelong antiretroviral therapy (ART) is the main treatment method to suppress the viral load. As HIV infection transitioned into a chronic disease, many comorbidities also threaten the health of PWH. One comorbidity is atherosclerotic cardiovascular disease (CVD), with the risk of developing CVD for PWH being about 2.16-fold higher than an uninfected individual regardless of ART status.

PWH also have greater gut dysbiosis with less beneficial and more harmful bacteria. This points to possible mechanisms of HIV infection driving CVD development, such as gut barrier disruption or production of metabolites that increase aortic lesions. Therefore, we aimed to investigate how the gut microbiome is altered and which species are involved in CVD development for PWH.

To study this, we transplanted human microbiota from fecal samples of HIV-positive and negative donors into atherosclerosis-prone mice to test aortic lesion development. First, we concluded that bacteria from human fecal samples can colonize the mouse gut. After 16 weeks of continued transplantation, we found that giving HIV-positive microbiota led to increased aortic lesions in mice. 16S rRNA analysis on feces of human microbiota receiving mice revealed that gut microbiome species in *Hungatella, Bacteroides,* and *Coprenecus* genus correlated with higher lesion scores, while species in *Romboutsia* genus correlated with lower lesion scores. These results show microbiome species that possibly connect HIV infection to CVD development for future investigations.

Infectious Disease

POSTER NUMBER:
116

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Superhydrophobic Bandages and Antimicrobial Photodynamic Therapy as an Innovative Approach to Tackle Third-Degree Burn Infections In Vivo

Investigators: N. K. Eidenschink, F. V. Cabral, O. Mooradian, A. T. Conn, Q. Xu, A. Lyons, A. Greer, T. Hasan

Third-degree burns are challenging, multifaceted injuries. This is compounded by the emerging issue of multidrug-resistant (MDR) bacteria which can lead to systemic complications or death. With the standard care of antibiotics becoming less effective in MDR bacteria, there is an urgent need for innovative treatment modalities. Antimicrobial Photodynamic Therapy (aPDT) is one established treatment method. Photosensitizers (PS) and illumination at specific wavelengths generate reactive oxygen species, such as singlet oxygen (1O2), to inactivate microorganisms. This therapy has demonstrated results against MDR bacteria, though the inability to deliver the PS presents limitations to the efficacy of aPDT.

Superhydrophobic (SH) aPDT is an appealing treatment which can address previous limitations by isolating PS inside a superhydrophobic polydimethylsiloxane (PDMS) bandage that delivers airborne singlet oxygen to the infected tissue upon light illumination, ensuring the infected area is treated uniformly. In this new technology, SH bandages are coated with the PS verteporfin, a constituent of FDA-approved visudyne. The bandages are equipped with built-in air channels to supply oxygen for aPDT and are specifically designed to ensure PS does not contact tissue directly. Our study evaluated the efficacy of SH-aPDT in vivo on third-degree burn wounds infected with Staphylococcus Aureus (Methicillin-Resistant) and treated using a red laser (690 nm) at various fluences. SH-aPDT successfully reduced the bacterial load and wound size in treated mice. Additionally, immunofluorescence staining revealed increased α-SMA expression and decreased COX-2 expression 10 days post-treatment. These findings suggest that SH-aPDT may promote wound healing while reducing inflammation in burn-infected wounds.

POSTER NUMBER:
117

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Investigating Shifts in Viral Entry of Emerging SARS-CoV-2 Variants

Investigators: O. T. Glover, J. Boucau, A. K. Barczak, POSITIVES (post vaccination viral characteristics study)

The Covid-19 pandemic remains an evolving threat as new viral variants emerge. SARS-CoV-2 entry is initiated upon engagement of the viral spike protein (S protein) by the angiotensin converting enzyme 2 (ACE2) receptor on host cells. In the primary, endocytic pathway of entry, gradual acidification of the endosome containing the viral particle activates cathepsin B and cathepsin L to prime the S protein for viral entry. A secondary pathway of entry for coronaviruses involves the serine protease TMPRSS2 interacting with the S protein, leading to direct fusion of the host cell and virus. Our current work builds on existing knowledge of viral entry to identify preferred entry mechanisms for emerging variants of interest. In a longitudinal study of SARS-CoV-2-infected outpatients we observed that JN.1 lineage strains were unable to infect Vero E6 cells in our cell culture model. Viral entry of JN.1 was restored in Vero cells expressing TMPRSS2 and ACE2. To explore shifts in entry accompanying SARS-CoV-2 evolution we compiled a panel of SARS-CoV-2 variants from WA1 to a recent subvariant of the JN.1 lineage, KP.3, and infected cell lines engineered to restrict available entry mechanisms. Tests of viral variant entry using these cell lines and studies using serine proteinase and late endosomal inhibitors supported a preference for TMPRSS2-mediated entry by JN.1 lineages compared to endocytic-driven entry by prior variants. A fundamental understanding of the relationship between lineage-specific viral entry pathway preference and pathogenicity could inform our understanding of future emergent variants of concern.

Infectious Disease

POSTER NUMBER:
118

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Presentation of RhCMV 68-1 vaccine-identified SIV epitopes by human and rhesus MHC-E

Investigators: X. Guo, L. Walters, C. Casquero, S. Cheevers, M. Birnbaum, B. Walkers

HIV continues to pose a global health challenge and has prompted extensive research exploring effective vaccine strategies. Previous breakthroughs in HIV vaccine development using a rhesus CMV vector recombinant for SIV antigen (RhCMV 68-1/SIV) showed unprecedented sterile immune clearance against SIV challenge. An unconventional, MHC-E-restricted subset of CD8+ T cells was shown to be necessary for protection. However, the majority of vaccine-identified SIV epitopes lacked canonical anchor residues, demonstrated low or negligible binding to human HLA-E, and did not support stable HLA-E/B2M complex formation in vitro. Peptide-interfacing residues of human and rhesus MHC-E binding grooves are highly conserved, and thus, these orthologues are predicted to bind peptides with a similar motif. However, a comprehensive analysis of RhCMV68-1/SIV vaccine-identified SIV peptide binding to rhesus MHC-E (Mamu-E) is currently lacking. Here, we present a direct comparison of human versus rhesus MHC-E thermostability in complex with vaccine-identified SIV epitopes using differential scanning fluorimetry. Similar to human HLA-E, only one vaccine-identified SIV epitope demonstrated significant stabilization of orthologous Mamu-E alleles. However, the degree of stabilization for both human and rhesus MHC-E was low, with melting temperatures (Tm) below body temperature, calling into question the physiological relevance of this interaction. The remaining vaccine-identified SIV epitopes provided no stabilization of HLA-E or Mamu-E orthologues, even when the peptides were supplied in molar excess and were not washed out before obtaining the Tm. This weak or insignificant stabilization challenges the role of putative MHC-E-restricted SIV epitopes in the molecular mechanism of RhCMV68-1/SIV vaccine-mediated protection.

Infectious Disease

POSTER NUMBER:
119

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Exploring the PREVENT HF Score and Myocardial Function among Persons with HIV

Investigators: M. Gupta, A. R. Walpert, S. Srinivasa, C. N. Dunderdale, H. H. Haptu, M. Manandhar, H. Lee, R. Y. Kwong

Persons with HIV(PWH) are at risk for myocardial structural changes, which can progress to diastolic dysfunction and heart failure with preserved ejection fraction (HFpEF). We explored the AHA PREVENT HF (Predicting Risk of cardiovascular disease EVENTs for Heart Failure) risk score in relation to cardiac magnetic resonance (CMR) imaging indices.

This cross-sectional study included 37 PWH on ART, ages 40-65, without known CVD who underwent CMR. The PREVENT HF risk score was assessed using the AHA PREVENT HF calculator. Scores were correlated to variables on CMR that are known indicators of subclinical myocardial dysfunction [left atrial volume index (LAVI), global longitudinal strain(GLS), and left ventricular mass index(LVMI)] and inflammation [extracellular volume(ECV) and T1].

PWH were 55(6) years, predominantly male(76%) and white(57%) with BMI in the obese range 31(5)kg/m^2. Median PREVENT HF score was 2.6(1.4,4.1)%. The PREVENT HF score correlated to LAVI (r=0.35, P=.04), T1(r=0.35, P=.04), IL-6(r=0.36, P=.03) and NT-proBNP(r=0.42, P=.01). Risk scores were higher for those meeting clinical cutoffs LAVI>34 mL/m^2 and T1e1250 ms. For predicting LAVI >34 mL/m^2, a PREVENT HF score of 2.5 was the optimal cutoff [sensitivity 85%, specificity 65%, AUROC 0.769 (P<.05)]. In predicting T1≥1250 ms, a PREVENT HF score 3.6 was the optimal cutoff [71% sensitivity, 95% specificity, AUROC 0.727 (P<.05)].

The PREVENT HF score related to indices of altered myocardial structure and inflammation among asymptomatic PWH with subclinical disease. These data begin to inform us about the utility of PREVENT HF score using radiographic findings, though more studies are needed among PWH to validate its use as a prediction tool.

POSTER NUMBER:
120

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Epitope-Driven Effector Functions of Broadly Neutralizing Antibodies Across Diverse HIV Isolates: Insights for Next-Generation Therapeutics

Investigators: C. J. Li, M. Phelps, J. M. Brady, A. D. Nitido, D. Lingwood, A. B. Balazs

Although antiretroviral therapy suppresses HIV replication, it does not eliminate latent reservoirs, allowing viral rebound upon treatment termination. Antibody-dependent effector functions, such as antibody-dependent cellular cytotoxicity (ADCC) and antibody-dependent cellular phagocytosis (ADCP), play a key role in clearing infected cells. However, how epitope specificity influences broadly neutralizing antibody (bNAb)-mediated effector functions across diverse HIV isolates remains unclear.

We evaluated 20 HIV bNAbs targeting distinct envelope epitopes and nine primary HIV isolates from diverse clades for innate immune activity. ADCC was measured using ZsGreen+ Env-expressing target cells incubated with bNAbs and CD16-expressing NK-92 cells, followed by flow cytometry analysis. ADCP was assessed by incubating THP-1 cells with target cells and bNAbs, quantifying phagocytosis via ZsGreen uptake.

Our results demonstrate that epitope specificity significantly affects bNAb effector function. V1V2-directed bNAbs strongly mediated ADCP, whereas MPER-directed antibodies predominantly induced ADCC. CD4bs- and V3-directed bNAbs exhibited robust activity in both functions. Notably, envelope variation influenced effector function engagement; for example, X1632 was resistant to ADCC, while CH119 exhibited reduced ADCP susceptibility. In contrast, JR-CSF and 25710 envelopes were highly responsive to both mechanisms. Furthermore, Fc-engineered bNAbs enhanced effector function potency.

These findings underscore the importance of epitope targeting in bNAb-mediated effector functions and demonstrate that Fc engineering can optimize antibody responses. This knowledge is critical for designing HIV immunotherapies and vaccines that effectively harness immune effector mechanisms for viral elimination.

Infectious Disease

POSTER NUMBER:
121

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Multi-agent immunosuppressive therapy for immune-related adverse event (irAE) treatment is associated with high rates of infectious complications

Investigators: T. L. Lim, D. Restifo, R. Merkin, S. Rouhani, M. Vilbert, B. Peacker, L. Zubiri, S. P. Hammond, K. Reynolds, Severe Immunotherapy Complications Team

Severe irAE treatment with multiple immunosuppressive therapies (ISTs) decreases morbidity and mortality. Nevertheless, infectious complications in this population are not well-studied. We thereby retrospectively studied patients who received an immune checkpoint inhibitor (ICI) and experienced at least one irAE requiring corticosteroids and at least two steroid-sparing ISTs administered within 90 days of each other. We annotated all infections from ICI start until 90 days post-ISTs. Opportunistic infections (OIs) included herpesvirus and invasive fungal infections. Risk factors were identified using Cox regressions adjusting for age at ICI initiation, sex, ICI regimen, ISTs, and steroid dose. 175 patients had 238 irAEs and 417 ISTs with a median follow-up of 367 days. The most common irAEs were colitis (n=67, 38%) and hepatitis (n=42, 24%). The most frequent ISTs were mycophenolate mofetil (n=92, 53%) and infliximab (n=77, 44%). 103 patients (59%) developed 223 infections. 87 patients (50%) underwent OI testing, of which 29 (33%) had 36 OIs, most commonly EBV DNAemia (n=14, 16%) and CMV reactivation (n=12, 14%). OI density per 1000 patient-days significantly increased after starting ISTs (1.70 vs 0.03, p=0.002). Non-OI and OI risk factors were anti-CD20 use (HR: 10.58, 95% CI: 3.64-30.72, p<0.001) and a max prednisone dose >100mg (HR: 2.89, 95% CI: 1.21-6.90, p=0.017), respectively. 58 patients (33%) had severe (requiring hospitalization or parenteral antibiotics) or life-threatening infections. 8 patients (5%) had fatal infections. Overall, multiple IST use for severe irAEs is associated with increased OIs and a 5% infection-related mortality rate. Screening and prophylaxis should be considered when appropriate.

POSTER NUMBER:
122

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Developing Viral Culture and Quantification Protocols to Assess Infection Dynamics of RSV and Influenza

Investigators: M. Mandal, J. Boucau, O. T. Glover, A. K. Barczak, POSt-VaccInaTIon Viral CharactEristics Study (POSITIVES) consortium

Respiratory Syncytial Virus (RSV) and seasonal influenza virus are leading causes of respiratory illness. Yearly, influenza is estimated to affect 1 billion people and contribute to 290,000-650,000 deaths. RSV infects 90 percent of children before the age of 3 and can cause particularly severe disease in individuals under 2 or older than 60. In previous work, we applied viral culture on samples from a longitudinal cohort study of individuals with COVID-19 infection to understand viral shedding over time post infection (POSITIVES study). Here, we extend this approach to influenza and RSV to ultimately evaluate how vaccination and interventions affect duration of infectiousness and overall viral dynamics. As culturing viable virus from nasal swabs may offer the best available lab-based proxy for infectiousness, establishing in vitro protocols for viral culture and quantification from swab samples is therefore critical. We thus sought to establish protocols to infect lung adenocarcinoma cells (A549). We confirmed flu infection using our optimized protocols by observing cytopathic effects at 24 hours post-infection, with detection of influenza A and B nucleoprotein expression by Western blotting. Infections of A549 cells with RSV-A and RSV-B were also successful, as confirmed by RSV nucleoprotein detection by Western blotting, despite no observed cytopathic effects even at 25 dpi. Focus-forming unit assays (FFUs) to quantify viral replication were then also attempted; H3N2 and RSV FFUs showed prominent foci at 24hpi. We will apply our optimized protocols to patient specimens to understand the dynamics of viral infection with flu or RSV, including emerging substrains.

Infectious Disease

POSTER NUMBER:
123

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Error Rate of Replication Sequencing (ERR-Seq) Reveals High Mutation Rate Variation Within and Across HIV-1 Strains

Investigators: A. D. Nitido, N. Omur, A. Jackson

A characteristic feature of HIV-1 is its ability to develop a diverse population that can adapt to hostile environments. The source of this diversity is often attributed to its high mutation rate, estimated to be around 5.0x10-5 mutations per site per round of replication (mut/site/rep). However, there is high variation in the observed mutation rates across published studies. It remains unclear to what extent these differences are a product of different experimental methods or natural variation in the mutation rate. To address this question, we developed a transduction-based method, coined Error Rate of Replication Sequencing (ERR-Seq), which measures the in vivo mutation rate and mutational profiles of HIV-1 on any template sequence.

We performed the ERR-Seq assay using the HIV-1 NL4-3 GagPol on an NL4-3 Env transgene template and observed high variation in the mutation rate with a mean rate of 7.2x10-5 mut/site/rep and a 95% confidence interval of 2.2x10-5 to 1.8 x10-4 mut/site/rep. We measured the mutation rate of 14 additional HIV-1 GagPols on the NL4-3 Env template, recapitulating a similar distribution of mutation rates. We evaluated the mutation rate on NL4-3 on 3 different HIV-1 Env templates and observed significant differences in the mutation rate across different locations in the various Env templates. Our data demonstrate high mutation rate variation across different HIV-1 strains and within replicate transductions of the same virus genotype. This suggests that there are yet to be described molecular factors (aside from template sequence context) that drive HIV-1 mutation rate variation.

POSTER NUMBER:
124

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ERR-Seq 2: HIV-1 Mutation Rate Measurement Using Long-Read Sequencing

Investigators: N. Omur, A. D. Nitido, A. B. Balazs

Upon infection, HIV-1 evolves into a diverse population that can develop resistance to potential therapies, including antiviral therapies and broadly neutralizing antibodies. To develop more effective individual therapies and therapeutic cocktails, we must better understand the molecular features that drive the evolutionary process. In particular, understanding the molecular basis of variation in the mutation rate of HIV may allow us to target said machinery therapeutically.

Previously, we developed Error Rate of Replication Sequencing (ERR-Seq), a method for mutation rate measurement that utilizes short-read sequencing technology. ERR-Seq measures the HIV mutation rate in the context of any Gag-Pol protein on a given template sequence.

Here, we present an updated ERR-Seq method that leverages long-read sequencing technology (coined ERR-Seq 2). ERR-Seq 2 utilizes molecular barcodes to track mutation accumulation across templates up to 4.5Kb in length. Utilizing a suite of molecular amplification methods and long-read sequencing, ERR-Seq 2 allows for high throughput amplicon error correction, allowing for the tracking of specific mutation events. This poster will present the ERR-Seq 2 optimization and preliminary data as we leverage this technology to probe the molecular mechanisms that regulate mutation rate variation in HIV.

Infectious Disease

POSTER NUMBER:
125

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Plasma Neurofilament Light Chain Suggests Advanced Neuronal Age in Cognitively Unimpaired People with HIV on Antiretroviral Therapy in ACTG A5322 (HAILO)

Investigators: H. Park, S. S. Mukerji, P. Bachanová, L. V. Rosen, P. Kivisäkk, R. Kashlan, F. C. Chow, K. Wu, R. M. Dastgheyb, L. H. Rubin, K. Tassiopoulos, E. P. Hyle, R. A. Parker, ACTG A5322

Background: Neurofilament light chain (NfL), a neuronal damage biomarker, could become routine in cognitive impairment assessments. Age is associated with plasma NfL values in people with HIV (PWH) and without (PWoH). We assessed plasma NfL values in cognitively unimpaired, older treated PWH and estimated accelerated aging, comparing their values to reference values from healthy PWoH.

Methods: This secondary analysis focused on cognitively unimpaired PWH ≥45y and eGFR≥60 mL/min/1.73m2. Cognitive status was determined using four neuropsychological tests. NfL were quantified using single-molecule array platform. Age-partitioned NfL reference values were defined using published data from 1,724 healthy PWoH (Simrén et al., 2022). A logistic regression model estimated the accelerated aging needed for only 5% of PWH to exceed the PWoH NfL cut-off, analogous to a dose-response approach.

Results: The study included 340 PWH (17% female, 29% non-white, median age 52y). Mean NfL concentration was 11.28 (5.56) pg/mL, with 24% above the 95% cut-off. To make NfL values comparable to PWoH, an age adjustment was added to the actual age until the proportion of PWH above the reference limit was <5%. We observed that PWH would need to be 11.64y older (95% CI: 10.96-12.31y) for results to match a 5% rate of elevated NfL in PWoH.

Conclusion: Elevated NfL predicts cognitive decline in vascular and Alzheimer's dementia. Our study suggests cognitively unimpaired treated PWH have NfL levels comparable to healthy PWoH 11-12 years older. NfL may indicate accelerated neuronal aging in PWH, warranting further longitudinal investigation to understand its role in older PWH.

POSTER NUMBER:
126

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Activation of Virulent Secretion System in Shigella

Investigators: L. Pham, P. Chen, M. Goldberg

Shigella flexneri (S. flexneri) is gram-negative bacteria that causes dysentery using the Type 3 Secretion System (T3SS) that encodes a membrane embedded needle apparatus to deliver virulence effectors into the host cytosol. Upon host sensing, S. flexneri T3SS secretes the translocases IpaB and IpaC, which insert into the host plasma membrane forming a translocon pore and enabling S. flexneri to dock and deliver effector proteins into the host cytosol. The translocon pore, the interior of which is lined by the first transmembrane domain (TM1) of IpaB, is a dynamic structure that participates in regulating T3SS effector secretion. We hypothesize that select transmembrane domain and cytosolic residues of IpaB and IpaC coordinate to form a dynamic pore plug when the translocon pore is membrane embedded. To characterize the mechanism of the translocon dynamics, we generated single cysteine substitution mutants of IpaB and IpaC and studied the positions of specific IpaB and IpaC residues in the context of assembled translocon pores using proximity-enabled crosslinking. Our data show that the IpaB TM1 residues facing the pore channel crosslink with the IpaC cytosolic residues we previously found to loop into the pore channel interior. Consistent with previous studies, the funnel-shaped translocon pore channel is wider towards the extracellular size of the plasma membrane but narrower towards the host cytosol. This structural information provides new insights on translocon pore assembly necessary for driving the translocation of effector proteins during S. flexneri infection.

Infectious Disease

POSTER NUMBER:
127

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Exposure of HIV envelope protein gp120 alone modulates hepatocyte dynamics and signaling.

Investigators: V. A. Spalding, B. A. Fellenstein, M. Xu, C. Warner, N. Alatrakchi, W. Lin, R. Chung, S. Salloum

Background: Recent evidence has suggested that HIV infection is a driver of hepatic fibrogenesis itself. We and others have demonstrated the critical role of Yes-Associated Protein 1 (YAP1) in regulating liver fibrosis in MASLD and HIV. The aim of this work is to further define how the HIV gp120 envelope protein interacts with the liver environment to drive fibrosis.

Methods: qRT-PCR and western blot were used to determine the response of Huh7 cells exposed to various HIV envelope proteins. Primary hepatocytes (pHH), primary hepatic stellate cells (pHSC), and a 3D spheroid system combining pHSC with Huh7 cells were also used to investigate this mechanism in vitro. In vivo samples were sourced from mice treated with gp120 over 12 weeks.

Results: Compared to DMSO, REV, and GAG; gp120 protein had a significant upregulation of YAP-related mRNA and protein in Huh7 cells. gp120 exposure in Huh7 cells also significantly upregulated lipid droplet formation pathways (ADM2, LDLR, PLIN2), which was reflected in extensive lipid droplet staining. pHSC directly exposed to gp120 produced no alterations in the expression of benchmark fibrosis genes (CTGF, αSMA, COL1A1). However, in a spheroid model where crosstalk with hepatocytes is facilitated, we observed substantial coregulation of both fibrogenic and YAP-related genes, in some cases stronger than that seen with full virus infection. pHH and mice exposed to gp120 generated moderate increases in the expression of YAP-related genes.

Conclusion: Early data from multiple lines of investigation suggest a compelling relationship between gp120 and YAP-related hepatic fibrogenesis post HIV infection.

POSTER NUMBER:
128

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Degradable Transgene via Modification of a Cre-Lox Recombination System as Regulatable Gene Therapy Vector

Investigators: J. M. Trinidad-Rivera, A. B. Balazs

Over the past decades, gene therapy has open the possibility of treating incurable diseases, such as primary immunodeficiency disorders, retinal degradation, hemophilia, AIDS, Parkinson's disease, amongst others. To date, over 3900 gene trials have been logged, and more are expected to be done, as gene-targeting technologies continue to improve and become more accesible. However, most gene therapy are only used as a last resort. Unlike prescribed drugs which can be stopped as needed, gene therapies are irreversible.

To tackle this complication brought by gene therapy, many systems have focused on ensuring that transgene expression only occurs in certain scenarios, such as with the used of tissue-specific promoters or inducible promoters. However, another way to deal with this problem is to generate a degradable transgene that would be eliminated by the recepient. In the context of vector immunoprophylaxis (VIP) via adeno-associated viral vector (AAV), the use of a Cre-Lox recombination could potentially be a apt system to generate a regulatable gene therapy.

However, the localization of the AAV episome in the nucleoli of cells has made it difficult to implement the Cre-Lox system. Here we prepose that the modification of an iCre constructs with a nuclear localization signal (NLS), with an seven arginine, converting it into a nucleolar localization signal (NoLS), will greatly increase the efficacy of the Cre-Lox system degradation.

POSTER NUMBER:
129

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Modeling the Value of Information and Implementation of a Study on HIV Pre-exposure Prophylaxis (PrEP) Toxicities Among Adolescents in the United States

Investigators: H. Zarei, C. Flanagan, P. Pei, A. Neilan

Objectives. Generic tenofovir-disoproxil-fumarate/emtricitabine (TDF-FTC) is cost-effective compared to tenofovir-alafenamide/emtricitabine (TAF-FTC) for HIV PrEP among young men who have sex with men (YMSM) in the US. However, 37% of providers prescribe TAF-FTC over TDF-FTC despite the high cost, potentially due to uncertainty around TDF-FTC toxicity among adolescents. We applied value of information (VOI) and implementation (VOM) frameworks to estimate the potential benefit of a clinical study on PrEP toxicities.

Methods. Using the CEPAC-Adolescent microsimulation model, we projected the incremental net monetary benefit (INMB=differences in health benefits and costs at a willingness-to-pay threshold) of decision-making before and after a hypothetical study on TDF-FTC bone fracture incidence rate. We considered 60,405 on-PrEP YMSM population over 5 years and two PrEP strategies: TDF-FTC and TAF-FTC. Inputs include TDF-FTC bone fracture incidence=1.87/100 person-years (range: 0-3.75); PrEP pre-/post-study uptake (TDF-FTC=63%/90%, TAF-FTC=37%/10%); age-stratified on/off-PrEP HIV incidence (0.4-6.4/0.6-10.1/100 person-years); PrEP adherence (46%); monthly costs (TDF-FTC=$85, TAF-FTC=$1,618). Projected outcomes include VOI (INMB of reducing PrEP toxicity uncertainty) and VOM (INMB of increasing cost-effective strategy uptake). Willingness-to-pay threshold is $100,000/quality-adjusted life-year (QALY).

Results. TAF-FTC is not cost-effective compared to TDF-FTC with incremental cost-effectiveness ratio of $3.2 million/QALY. Even if TDF-FTC toxicity uncertainties were eliminated, TDF-FTC would remain the cost-effective strategy, implying VOI equals zero. Improving TDF-FTC uptake would yield a VOM of $5.7 billion over 5 years.

Conclusions. While a study reducing PrEP toxicity uncertainty would not change the decision to adopt TDF-FTC for YMSM, there is value in scaling up TDF-FTC implementation, leading to >$1.1 billion potential annual savings.

Neurosciences

POSTER NUMBER:
130

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Radiomics Derived Brain Age Influences Patient Reported Outcomes After Acute Ischemic Stroke

Investigators: L. Angeleri, E. Lindgren, R. Regenhardt, N. Rost, M. Schirmer

Objective: To investigate the relationship between radiomics derived brain age and Patient Reported Outcome Measures (PROMs) in acute ischemic stroke (AIS) patients.

Background: Radiomics-derived brain age provides a quantitative evaluation of brain health leveraging features of neuroimaging imperceptible to the human eye. Brain Age Gap (BAG) measures the difference between biological brain age and chronological age. Higher BAG has been associated with worse functional outcome as measured by the clinician-rated modified Rankin Scale (mRS). Considering growing emphasis placed on patient reported outcomes, the association between BAG and PROMs remains to be evaluated.

Design/Methods: Patients with AIS, T2-FLAIR MRI imaging, and PROMs from the COAST cohort (single center, 2017-2020) had BAG calculated using our radiomics-based brain age estimation pipeline. Outcomes were defined by mental (TMental) and physical (TPhysical) scores based on responses to the PROMIS Global Health questionnaire (Range: 0-100). Association between poor outcome (T-score <50) and BAG was modeled using logistic regression adjusting for age, sex, and NIHSS score.

Results: A total of 132 patients were analyzed (41% Female; median(IQR): Age 64(57-71), NIHSS 2(1-5), TMental 48.3(43.5-53.3), TPhysical 47.7(42.3-54.1)) with 75 and 76 patients having poor outcomes for TMental and TPhysical, respectively. Higher BAG was associated with worse TMental (aOR=1.71, 95%CI=1.17-2.58, p<0.01), but had no significant impact on TPhysical scores (aOR=1.20, 95%CI=0.82-1.78, p=0.35).

Conclusion: Patients with a larger positive BAG —reflecting older appearing brains— reported worse mental, but not physical, health outcomes after AIS. Our results support including brain age in clinical prognostication and future research into patient-centered outcomes after AIS.

POSTER NUMBER:
131

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RANBP1 causes splicing-independent STMN2 loss in TDP-43 proteinopathy

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The RNA-binding protein TDP-43 plays a key role as a splice repressor and its nuclear loss in amyotrophic lateral sclerosis (ALS) leads to aberrant mis-splicing of hundreds of neuronal transcripts and the inclusion of non-conserved intronic sequences, referred to as cryptic exons (CE). Most transcripts with CEs are reduced in their expression via nonsense mediated decay or other RNA degradation pathways. Stathmin2 (STMN2), an essential protein for axonal regrowth and stability, is by far the most downregulated of these transcripts; this raises the possibility that additional pathways may cause STMN2 reduced expression beyond CE-dependent premature polyadenylation. To identify the pathways underlying STMN2 downregulation in FTD/ALS, we performed a FACS-based genome-wide CRISPR interference screen in human iPSC-derived neurons expressing endogenously tagged STMN2-mScarlet. Here we show several pathways modifying STMN2 expression and highlight the top negative hit RANBP1, a Ras-related nuclear (Ran) binding protein involved in nucleocytoplasmic transport that is also misspliced upon TDP-43 loss. Specifically, we describe how RANBP1 loss dramatically decreases STMN2 transcription in iNeuron models and in postmortem brain samples. With this, we offer a new model to explain the strong STMN2 downregulation upon TDP-43 nuclear loss: one known, direct pathway where TDP-43 loss drives STMN2 CE formation and a secondary, indirect pathway whereby TDP-43 loss impacts RANBP1 expression and drives reduced STMN2 transcription.

POSTER NUMBER:
132

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Integrating Effective and Structural Connectivity in the Human Brain

Investigators: A. S. Atalay, M. Fecchio, B. L. Edlow

Effective connectivity, the influence that one brain region exerts on another, is key to understanding brain function in normal and pathological conditions. Transcranial magnetic stimulation with simultaneous electroencephalography (TMS-EEG) has been used extensively to assess effective connectivity in psychiatric and neurological disorders by perturbing cortical nodes within widely distributed brain networks. However, the underlying structural network properties that sustain the propagation of TMS-evoked potentials within these networks are not fully understood. To enhance mechanistic understanding of effective connectivity in the human brain, we created a tool that links high-temporal resolution TMS-evoked potentials (TEPs) with high-spatial resolution structural connectomes. Our tool, Surface to Tractography Real-time EEG Activation Mapping in 4 Dimensions (STREAM-4D), integrates electrophysiologic source estimation models from TEPs with tractography models of structural connectivity from diffusion MRI. This integration is assessed qualitatively using Blender, an open-source 3D animation suite, and quantitatively through an activation-weighted structural connectivity analysis. In a proof-of-principle application to the study of effective connectivity, we used STREAM-4D to analyze TMS-EEG and diffusion MRI tractography data in a neurotypical subject across three stimulation sites: premotor, parietal, and occipital cortex. STREAM 4D revealed extensive structural connections activated by the TMS-evoked electrical waves, involving thalamocortical, ipsilateral cortico-cortical, and transcallosal cortico-cortical connections. Effectivity-weighted structural connectivity differed for the three stimulation sites, but two anatomic regions showed extensive connectivity for all three stimulation sites: the ipsilateral thalamus and putamen. These observations provide evidence that STREAM-4D reveals previously unseen relationships between structural networks and TMS-EEG.

POSTER NUMBER:
133

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Maternal TLR7 activation induces maternal autoimmunity, resulting in male-biased immune and ASD-like behavior alterations

Investigators: I. M. Bankowski, M. Slamin, I. R. Bishnoi, H. A. Norris, E. A. Bordt

Immune alterations, including maternal infection and autoimmunity during pregnancy, play significant roles in the etiology of autism spectrum disorder (ASD) etiology. Single-stranded viruses that activate toll-like receptor 7 (TLR7) are amongst the prenatal infectious agents most strongly linked to an increased risk for ASD. In this study, we examined whether maternal TLR7 stimulation via a TLR7 agonist (imiquimod, IMQ) during pregnancy could induce maternal autoimmunity. Furthermore, as prenatal exposure to maternal autoantibodies has been correlated with ASD diagnoses, we explored whether induction of maternal autoimmunity could transfer to offspring, resulting in offspring behavioral and immune alterations.

Pregnant dams were administered four IMQ or vehicle treatments. Maternal and offspring serum was collected, and offspring social communication was assessed through maternal separation-induced ultrasonic vocalizations (USVs). IMQ treatment was shown to elevate proinflammatory cytokines (indicating immune activation) and antinuclear antibodies (indicating autoimmunity) in maternal serum. Analyses of offspring serum cytokines and behaviors suggested that male offspring of IMQ-treated mothers showed preferential transfer of maternal autoantibodies and emitted fewer USVs, hinting at a male-biased vulnerability.

Building on our preliminary data, we are investigating whether prenatal treatment with an anti-inflammatory corticosteroid, dexamethasone, diminishes the male-biased IMQ-induced alterations. We are treating dams with dexamethasone one hour after each of the four IMQ or vehicle injections. Analyses to evaluate effects of dexamethasone on offspring behavior and cytokine are currently in progress. This research will provide critical insights into the impact of TLR7-induced maternal autoimmunity on sex-biased offspring neuroimmune behavioral as well as exploring potential therapeutic targets.

POSTER NUMBER:
134

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Dynamic pupillometry and live neutrophil function in infection-associated chronic conditions (IACC)

Investigators: E. M. Barringer, S. Akera, D. Saadi, M. Murakami, M. VanElzakker

In infection-associated chronic conditions (IACC), a subset of individuals never fully recover from an acute infection, reporting ongoing symptoms that onset with the initial infection. A well-known contemporary IACC is long-COVID. Even before the COVID-19 pandemic, patients with persistent symptoms beginning with an apparent infection were given the diagnosis of ME/CFS (myalgic encephalomyelitis/chronic fatigue syndrome). Despite differences in the initiating pathogen, there are multiple shared symptoms between long-COVID and ME/CFS including autonomic dysfunction, headaches, photophobia, sleep problems, general inflammatory "sickness" symptoms, post exertion malaise, and cognitive dysfunction.

Given these shared symptoms, an important research question is the extent to which disease mechanisms are shared across IACCs with different onsets. Here, we collect autonomic and immune-related measures from long-COVID, pre-COVID ME/CFS, and healthy control individuals using simple and inexpensive techniques that may increase access to community hospitals and house-bound patients.

To address this question, we conducted dynamic pupillometry, followed by a blood draw. Pupillometry involves a hand-held device to measure the pupil's response to a flash of light as a simple measure of neuroautonomic function, intercranial pressure, and photophobia. As a sensitive proxy for in-vivo immune dysfunction, we analyzed the activity of isolated live (never frozen) neutrophils using fresh blood. A microscope-slide-based microfluidic maze enabled measurement of several neutrophil functions including NETosis, motility, chemotaxis, and phagocytosis. Here we show how these approaches offer the potential of accessible, inexpensive testing to compare and assess autonomic and immune dysfunction across different forms of IACCs.

POSTER NUMBER:
135

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Neuropathological Correlates of Plasma GFAP Levels in Alzheimer's Disease and Related Dementias

Investigators: C. R. Bianco, H. Fatima, S. E. Arnold, P. Kivisäkk, A. Serrano-Pozo

Blood-based (plasma or serum) biomarkers have emerged as promising tools for the early differential diagnosis and prognostication of Alzheimer's disease (AD) and AD-related dementias (ADRD). While blood amyloid-beta (Abeta) and phospho-tau (pTau) levels reflect the Abeta plaques and pTau neurofibrillary tangles that define AD, blood glial fibrillary acidic protein (GFAP) levels are thought to represent brain reactive astrogliosis against plaques and tangles. Importantly, reactive astrogliosis has been recently implicated in the neurodegenerative process underlying AD/ADRD. Yet whether blood GFAP levels correlate with the severity of brain reactive astrogliosis, cortical atrophy, and/or AD neuropathological burden remains uncertain.

We investigated the neuropathological correlates of plasma GFAP levels in a large cohort of brain donors with AD/ADRD who had participated in our Massachusetts Alzheimer's Disease Research Center Longitudinal Cohort study. Plasma GFAP, pTau181, pTau217, and neurofilament light-chain (NFL) levels were measured with MSD assays in one or more blood samples collected during life. GFAP-, Abeta-, and pTau-immunoreactive area fraction as well as cortical thickness were measured in postmortem brain sections from multiple brain regions of the same individuals using a quantitative immunohistochemistry pipeline. Statistical analyses consisted of mixed effect models with plasma GFAP levels as outcome variable, each neuropathological measure as independent variable, adjusting for age, sex, and interval between blood sampling and death/autopsy.

Here we show that plasma GFAP—but not pTau181, pTau217, or NFL—levels independently correlated with postmortem frontal cortex GFAP-immunoreactive area fraction. Thus, we conclude that plasma GFAP is a reliable biomarker of brain reactive astrogliosis.

POSTER NUMBER:
136

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Characterizing the Role and Mechanisms of Gene Fusion in Amyotrophic Lateral Sclerosis

Investigators: A. Boudi, T. Petrozziello, H. Xu, S. S. Huntress, J. Lemanski, B. Jana, M. Kesavan, A. Shahryari, A. L. Castillo-Torres, R. Z. Monsanto, C. E. De Esch, J. D. Berry, M. E. Cudkowicz, R. M. Pinto, M. Talkowski, D. Gao, G. Sadri-Vakili

Objectives: We previously identified an enrichment of gene fusion events in amyotrophic lateral sclerosis (ALS) post-mortem brain and spinal cord using publicly available RNA-Seq datasets. Here, we assessed the molecular consequences of one of the most recurrent fusion: YY1 Associated Factor 2 (YAF2)-RING1 and YY1Binding Protein (RYBP). Both genes are involved in chromatin remodeling and transcriptional regulation via histone H2 ubiquitination (H2AK119ub1) and polycomb group (PcG) protein interactions.

Methods: RNA-Seq was performed in a larger cohort. Human neuroblastoma SH-SY5Y cells were transfected with YAF2, RYBP or YAF2-RYBP constructs. Immunocytochemistry, assay for transposase-accessible chromatin with sequencing (ATAC-Seq) and RNA-Seq were conducted to assess PcG proteins interactions, chromatin accessibility, and transcriptional changes respectively.

Results: We identified 815 fusion events, 426 specific to ALS. Our results revealed that YAF2 and RYBP interact with PcG proteins in SH-SY5Y cells. YAF2-RYBP showed increased colocalization with RING1A and a significant reduction in H2AK119ub1 levels, suggesting alterations in chromatin accessibility and transcription. ATAC-Seq analysis revealed 38 differential transcription factor footprints altered by YAF2-RYBP. Gene ontology (GO) analysis highlighted changes in the GO term “photodynamic therapy-induced unfolded protein response”. We observed reduced binding of the transcription factors OTX2 and PITX2 to the TRIB3 promoter due to YAF2-RYBP. Lastly, RNA-seq revealed several differentially expressed genes, with four uniquely altered by YAF2-RYBP: PLEKHH1, SGIP1, PLPP3, and H1F0.

Conclusions: These findings highlight gene fusion enrichment in ALS and demonstrate that YAF2-RYBP alters chromatin accessibility and gene expression. These dysregulations may contribute to ALS pathogenesis, providing new insights into disease mechanisms.

Neurosciences

POSTER NUMBER:
137

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Measuring phosphorylated tau as a biomarker for amyotrophic lateral sclerosis

Investigators: A. L. Castillo-Torres, T. Petrozziello, A. Krishnamoorthy, R. A. Donahue, B. Fillingham, S. S. Huntress, B. L. Hammerschlag, P. Kivisäkk, S. E. Arnold, M. E. Cudkowicz, M. A. Garrett, L. B. Chibnik, J. D. Berry, G. Sadri-Vakili

Understanding the molecular mechanisms underlying amyotrophic lateral sclerosis (ALS), a fatal neurodegenerative disease, could provide beneficial insight not only in identifying suitable therapies, but also useful biomarkers that could hasten diagnosis, which, to date, could take up to two years. We and others have recently demonstrated a significant decrease in the ratio between the microtubule-associated protein tau (t-Tau) and its phosphorylated form at T181 (pTau-T181) in cerebrospinal fluid (CSF) derived from people living with ALS. Additionally, we also reported an increase in t-Tau levels in CSF derived from people living with bulbar onset-ALS. Lastly, we found that CSF tau levels correlated with faster disease progression, further supporting a role for t-Tau as a potential biomarker in ALS. Building on these findings, we assessed t-Tau, pTau-T181 levels and pTau-T181:tau ratio in plasma derived from a large cohort of people living sporadic ALS (sALS) as well as plasma from C9ORF72 gene-positive asymptomatic individuals. Our results revealed that while t-Tau levels were decreased in sALS plasma, pTau-T181 levels and pTau-T181:tau ratio were significantly increased. No changes were instead reported in C9ORF72 gene-positive asymptomatic individuals compared to healthy controls. Collectively, our results suggest that plasma and pTau levels could serve as biomarkers for sALS.

POSTER NUMBER:
138

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Cellular Mechanisms of Early Brain Overgrowth in Autistic Children: Elevated Levels of GPX4 and Resistance to Ferroptosis

Investigators: S. Chen, A. Shcherbina, S. T. Schafer, Z. A. Mattingly, J. Ramesh, C. Narayanan, S. Banerjee, B. Heath, M. Regester, I. Chen, S. Thakurela, J. Hallmayer, R. O'Hara, M. Solomon, C. W. Nordahl, D. G. Amaral, S. Chetty

Autistic individuals with disproportionate megalencephaly (ASD-DM)—characterized by enlarged brains relative to body height—experience higher rates of intellectual disability and more severe cognitive challenges compared to autistic children with average brain sizes. However, the cellular and molecular mechanisms underlying this neurophenotype remain poorly understood. To investigate these mechanisms, we generated human induced pluripotent stem cells (iPSCs) from typically developing non-autistic children and autistic children with and without disproportionate megalencephaly. These children were assessed longitudinally from ages two to twelve years using magnetic resonance imaging (MRI), cognitive testing, and medical evaluations. Our findings reveal that neural progenitor cells (NPCs) derived from ASD-DM children exhibit increased survival rates and suppressed cell death, despite experiencing heightened oxidative stress and ferrous iron accumulation. Notably, ASD-DM NPCs actively evade apoptosis and ferroptosis by regulating key proteins, including caspase-3 (CASP3), poly(ADP-ribose) polymerase 1 (PARP1), and glutathione peroxidase 4 (GPX4). Further supporting a ferroptotic signature, we observed elevated expression of cellular and peripheral selenocysteine genes, including GPX4, in ASD-DM children, suggesting activation of antioxidant mechanisms. Additionally, peripheral GPX4 and other selenocysteine gene expression levels correlated with cognitive outcomes (IQ), indicating potential diagnostic and prognostic value. These findings highlight ferroptosis as a key mechanism in autism spectrum disorder, offering insights into potential biomarkers and therapeutic targets for intervention.

POSTER NUMBER: 139

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Post-translational Modification Mimetics of Tau Reveal Patterns Of Aggregation And Liquid-liquid Phase Separation

Investigators: J. E. Chun, D. Sivasankaran, N. Quittot, J. M. Dubach, Z. Fan, B. T. Hyman

The protein Tau is known to misfold into well-defined fibril structures that are disease-specific and regroup more than 20 neurodegenerative diseases termed 'tauopathies'. While Tau fibrils have been well studied and characterized, the underlying mechanisms behind aggregation remain unclear. In this study we aim to determine Alzheimer's Disease (AD)-relevant factors of tau for aggregation, such as post-translational modifications (PTMs), in hopes to uncover which are responsible for aggregation and if these factors contribute to Tau's ability to undergo liquid-liquid phase separation (LLPS), a proposed intermediary step for Tau aggregation. To investigate critical factors for aggregation and LLPS, we produced a variety of recombinant Tau protein: unmodified, with AD-relevant PTM mimetics, and fragments of Tau known to form AD-relevant fibrils. Time-course Thioflavin T (ThT) assays were used in parallel with in vitro droplet assays to specifically investigate the relationship between amyloid fibril formation and LLPS propensity, respectively. Formation of fibrils was confirmed by negative-stain transmission electron microscopy. Through in vitro studies, we found that increased PTM mimetics of Tau prevented both fibrillization and LLPS, suggesting that a large net negative charge alone is not enough to induce the aggregation of Tau. In future studies we hope to explore how specific subsets of PTMs or heterotypic interactions with proteins/lipids mediate or modulate Tau self-assembly. We also hope to observe the transition from Tau liquid droplets to misfolded aggregates, providing further insight into the mechanistic details of Tau aggregation.

POSTER NUMBER: 140

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Normal Development of the Fetal White Matter Crossroads

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The fetal brain white matter crossroads, where axonal pathways intersect near the ventricles, appear as T2 hyperintense regions on Magnetic Resonance Imaging (MRI). Mapping their volumetric changes is key to understanding normal neurodevelopment.

This project was IRB-approved and HIPPA-compliant. We performed a cross-sectional volumetric analysis of normal fetuses that were prospectively recruited. Inclusion criteria: gestational age (GA) between 23-35, normal 2nd trimester US and standard prenatal evaluations. Exclusion criteria: MRI contraindications, claustrophobia, twin pregnancies. We performed manual segmentations on a publicly available spatio-temporal MRI atlas to automate processing. We segmented four crossroads: two frontal (F1, F2), one parietal (P), and one occipital (O). For each fetus, we generated a 3D T2 image using a super-resolution algorithm and propagated atlas labels via diffeomorphic registration, followed by manual review. GA was analyzed as a predictor of crossroad volume, with sex and laterality as covariates. We also calculated the percentage change in volume over time relative to total brain volume (TBV).

We analyzed 117 fetal MRIs (41 female; median GA: 30 weeks). Volume correlated with GA for all crossroads except right F1, with the strongest associations for left F2 (rho = 0.85), right O (rho = 0.80), and left O (rho = 0.76). GA positively associated with F2, P, and O ($P<0.001$). While absolute volumes increased with GA, their proportion relative to TBV decreased.

Here we show significant GA-related volumetric changes in the fetal crossroads, highlighting dynamic neurodevelopment. We provide a foundation for linking prenatal imaging with long-term brain health.

Neurosciences

POSTER NUMBER:
141

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The role of cognitive function in upper extremity motor impairments after stroke

Investigators: J. A. DiCarlo, A. Jaywant, N. Ward, D. J. Lin

While measures of upper limb motor impairment after stroke are traditionally thought to represent injury to the motor system, emerging evidence suggests a role for cognitive function. We aim to investigate the relationship between subdomains of cognitive function and upper limb motor impairment measures in sub-acute stroke, and to examine patterns of neural injury associated with each of these deficits. We assessed 56 individuals with upper limb hemiparesis (age 58.1±13.9, 67.8% male) 3 months post-stroke. Motor impairment was measured using the Fugl-Meyer Assessment (FMA) and Shoulder Abduction Finger Extension (SAFE) muscle strength scale. Cognitive function was assessed using the Montreal Cognitive Assessment (MoCA), from which executive function, attention, memory, and language subscales were extracted. Lesion volume and corticospinal tract injury were calculated from stroke lesions. Multiple linear regression examined the relationship between executive/attention function and motor impairment, controlling for lesion load and size. Voxel-based lesion-symptom mapping (VLSM) identified lesion patterns linked to motor and cognitive impairments. Global cognitive function explained over 20% of variance in motor impairment (FMA: R^2=0.21, p=0.003; SAFE: R^2=0.26, p<0.001). Executive (p<0.001) and attention (p=0.015) subscales correlated with motor impairment, while language (p=0.30) and memory (p=0.18) did not. VLSM analysis revealed substantial overlap (44.9% of significant voxels identified overlapped) between injury patterns linked to motor impairments and executive/attention dysfunction, particularly in the dorsolateral frontal cortex and anterior insula. Cognitive function, and particularly executive function and attention, are associated with upper extremity motor impairment post-stroke. These findings highlight the need for integrated cognitive-motor assessments in stroke rehabilitation.

POSTER NUMBER:
142

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Transcranial Magnetic Stimulation Improves Brain Network Functional Connectivity in a patient with Posterior Cortical Atrophy

Investigators: A. Du, T. Paranhos, B. Wong, N. Watson, D. Hochberg, M. Quimby, Y. Katsumi, B. Dickerson, M. Eldaief, A. Touroutoglou

Background: Posterior cortical atrophy (PCA) is a clinical syndrome characterized by visuospatial and visuoperceptual symptoms arising from neurodegeneration of the posterior temporoparietal and occipital cortices. Focal neuromodulation such as repetitive transcranial magnetic stimulation (rTMS) can change resting-state functional connectivity in a network-specific manner.

Objective: To investigate whether intermittent theta burst stimulation (iTBS) (a form of rTMS), can selectively modulate resting-state functional connectivity (FC) in posterior nodes of the default mode network (DMN) in a patient with PCA with amnestic symptoms.

Methods: A stimulation target within the left caudal middle frontal (cMFG) was defined based on the maximum FC with the DMN. This target was then stimulated with iTBS in a double-blind placebo-controlled paradigm. Changes in the FC of the stimulation target was used as the outcome measure.

Results: Following active stimulation, the patient exhibited selective increase in functional connectivity between the stimulation target and the DMN.

Conclusion: This case report provides novel evidence that network rTMS targeting using individualized resting-state fMRI can increase network FC in a patient with PCA. Larger controlled trials are needed to determine the impact of neuromodulation on cognitive performance in PCA and to further explore changes in DMN functional connectivity as a mechanism of these effects.

POSTER NUMBER:
143

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MEK Inhibition as a Potential Therapeutic Strategy for the Non-Tumor Manifestations of Neurofibromatosis Type 1 (NF1)

Investigators: A. Dyson, J. N. Bilchak, G. O. Suarez, N. C. LoRocco, J. Shahryari, S. Plotkin, S. Tomchik, M. S. Kayser, J. Walker

Neurofibromatosis type 1 (NF1) is a neurodevelopmental condition arising from loss-of-function mutations in the NF1 gene. Whilst commonly classified as a tumor-predisposition syndrome, up to 80% of affected individuals also display some form of behavioral and/or cognitive impairment, including specific learning difficulties, sleep disturbances, and autism spectrum disorder. Although the MAPK/ERK kinase (MEK) inhibitor selumetinib was recently approved for the treatment of inoperable plexiform neurofibromas in NF1, there are currently no treatments available for the aforementioned neurological symptoms. Whether MEK inhibition similarly provides a suitable therapeutic strategy in this context is unclear.

The Drosophila (fruit fly) genome contains a highly conserved ortholog of human NF1 (dNf1), knockout of which gives rise to numerous phenotypes reminiscent of the clinical condition. Thus, fly models of NF1 provide valuable systems with which to investigate potential therapeutic targets for the disorder. Here, we use CRISPR technology to generate novel dNf1 mutant alleles that recapitulate established dNf1-/- phenotypes, including reduced growth, cognitive deficits, tactile hyper-responsiveness, excessive grooming, circadian rhythm disruption, and impaired courtship. Pan-neuronal knockdown of MEK via RNA interference rescues these defects, supporting MEK inhibition as a potential therapeutic strategy for the behavioral symptoms of NF1 in the clinic. Efforts to determine whether pharmacological (as opposed to genetic) inhibition of MEK can also improve dNf1-/- behavioral phenotypes are currently ongoing.

POSTER NUMBER:
144

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Tau's Dual Role: Alzheimer's Disease by Antimicrobial Defense

Investigators: S. Ehricke, A. S. Rodriguez, M. T. DeFao, R. E. Tanzi, W. A. Eimer, Genetics and Ageing Research Unit

Alzheimer's disease (AD) is a growing concern in an aging population. Despite the identification of hallmark lesions (hyperphosphorylated tau [p-tau] and amyloid beta 42 [Aβ42] aggregates) over a century ago, effective treatments remain elusive. Recent epidemiological data, animal studies, and in vitro models suggest a link between pathogen infections, particularly Herpes simplex virus (HSV1), and AD pathology. Intriguingly, Aβ42 exhibits protective effects against HSV1, supporting the antimicrobial protection hypothesis, which posits that a dysregulated innate immune response contributes to AD.

Here, we utilized human 3D neuronal cultures to investigate the interaction between p-tau and microbial infection. Cultures were infected with HSV1 or bacteria, followed by immunocytochemical staining, confocal imaging, and MSD assays. Tau binding to microbial surface proteins was assessed using a modified ELISA, while tau aggregation and localization were examined with TEM. Additionally, tau propagation was analyzed using microfluidic devices.

We observed that synthetic p-tau was protective against HSV1, inhibiting infection and reducing plaque size and plaque count. Further, p-tau directly bound HSV1 capsid proteins in a concentration-dependent manner, while HSV1 infection promoted p-tau release, aggregation, and neuritic dystrophy. Bacterial infection similarly accelerated p-tau formation.

These findings suggest that tau hyperphosphorylation and aggregation may have evolved as an orchestrated immune response to brain infection. Furthermore, recurrent infections, immune dysregulation, or impaired clearance may all drive AD pathology. As we continue to decipher the etiology of AD, the involvement of pathogens and the innate immune system warrant even stronger consideration of antiherpetic treatments and vaccination for AD prevention.

POSTER NUMBER:
145

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Portable, Low-Field MRI for Alzheimer's Disease: Detecting Patterns of Atrophy Using Machine Learning

Investigators: A. Farnan, A. J. Sorby-Adams, J. Guo, P. Laso, A. E. Desenna, J. E. Kirsch, J. Zabinska, J. Dickson, L. Ramirez Gomez, P. Schaefer, S. Payabvash , A. De Havenon, M. S. Rosen, K. N. Sheth, J. E. Iglesias, T. Gomez-Isla, W. T. Kimberly

Magnetic resonance imaging (MRI) can be used to monitor disease progression in Alzheimer's disease (AD). Portable, low-field (LF) MRI enables point-of-care imaging directly in the clinic, and when combined with machine learning (ML) pipelines, can be used to quantify brain morphometry. To evaluate accuracy of LF-MRI and ML pipelines relative to conventional high-field MRI (HF-MRI; 1.5-3 T) and differentiate between AD and non-AD subjects, we enrolled patients with mild cognitive impairment (MCI; n=31) or dementia due to AD (n=24) from the Massachusetts General Hospital Memory Disorders Unit. A separate cohort of patients with vascular comorbidities (VC) of comparable age (n=22) were recruited from the Yale New Haven Hospital. LF-MRI was acquired on a 0.064 T MRI scanner, with HF-MRI obtained within 7±11 months of LF-MRI acquisition. T2 FLAIR sequences were processed through the ML pipeline "WMH-SynthSeg", which automatically generated volumes for 16 cortical and subcortical regions of interest. Correlations between HF and LF derived brain volumes were high across all structures (all $r>0.65$; $p<0.05$). MCI and AD patients showed regional atrophy relative to the VC cohort (all $p<0.05$), except for the caudate and 4th ventricle ($p>0.05$), with the greatest atrophy observed in the gray matter cortex, hippocampus, and amygdala (6%, 15%, and 18%, reduction compared to the VC, respectively; all $p<0.001$).This work highlights that LF-MRI acquisition, combined with ML algorithms, can generate brain volumes comparable to those derived from conventional MRI. Moreover, LF-MRI can differentiate between AD and non-AD patients, which may assist with diagnosis and monitoring of disease progression.

POSTER NUMBER:
146

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Short-interval common game play distinguishes people with and without cognitive impairment

Investigators: J. A. Galler, L. Yang, C. Wu, C. Young, E. Guzman-Velez, A. Bannon, H. H. Dodge, J. A. Gerber, S. E. Arnold

Background: Digital technologies are increasingly used to monitor neuropsychological functioning, but still require active effort and formal engagement. For a more naturalistic assessment of cognition and its daily variability, we adapted enjoyable tablet games to passively capture neurocognitive functioning. This study evaluated two weeks of MIND GamePack© play and compared this to cognitive function as assessed with standardized neuropsychological testing.

Methods: MIND GamePack© includes four iPadOS games: Memory Match (pair matching), Word Scramble (Boggle), FreeCell (Solitaire), and Block Drop (Tetris). Sixty participants were included: 37 with normal cognition (CN) and 23 with impaired cognition (CI: Mild Cognitive Impairment [MCI] or mild dementia [MD]). Participants were encouraged to play each game for ≥5 minutes/day, 5 days/week. Ten gameplay features were analyzed using Wilcoxon rank sum tests, with Spearman's correlations validating digital biomarkers against Repeatable Battery for the Assessment of Neuropsychological Status (RBANS) and Trail Making Test (TMT).

Results: Nine of ten features differentiated CN from CI. As expected, Memory Match - Percent Accuracy correlated with RBANS Immediate & Delayed Memory Indices (r = 0.60–0.75). In Block Drop, Hard Drops were associated with TMT A & B (r = -0.61 to -0.71). In Word Scramble, Word Score was correlated with RBANS Language Index (r = 0.5).

Conclusions: MIND GamePack© features effectively distinguish CN from CI individuals within two weeks, capturing differences in memory, language, and executive functioning. MIND GamePack© games may be useful tools to track daily cognition over time in clinical research, sensitively detecting decline, stability, or response to interventions.

Neurosciences

POSTER NUMBER:
147

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Investigating Blood-Brain Barrier Functionality in ACTA2 Multisystemic Smooth Muscle Dysfunction Syndrome (MSMDS)

Investigators: V. Krishnan, S. Mitra, S. Das, N. E. Uribe Ruiz, P. Kalailingam, R. Bennett, P. L. Musolino

MSMDS is an ultrarare monogenetic disorder caused by the missense mutation of arginine 179 replaced by histidine. The disorder is characterized by smooth muscle myopathy multisystemically with major dysfunction in the cerebrovascular system, involving vessels of all sizes and leads to strokes and white matter injury in childhood. Ischemic strokes commonly occur during episodes of hypotension or anesthesia suggesting severe impairment of cerebral autoregulation and neurovascular coupling. However, characteristics of its impacts on the blood-brain barrier (BBB) remain unknown.

To study its effects on the BBB, pericytes were isolated from the conditional knock-in mouse model (Myh11-Cre:Acta2R179fl/+), and primary endothelial cells to create an in-vitro BBB model. In-vivo, two-photon microscopy (2P) was employed to visualize BBB leakage using fluorescent dextran and to quantify blood flow velocity, baseline pulsatility, and functional hyperemia. Histological analysis was performed to assess BBB integrity, looking for signs of leakage, vessel damage, and neurovascular remodeling. To correlate our findings with patient data, perfusion maps and MRIs were analyzed to identify vessel stenosis and straightening.

Here we show accelerated neurodegeneration observed in the mouse model, displaying histopathological features similar to those seen in neuronal proteinopathies. The in-vitro BBB model showed differences in integrity, with consistent trans-endothelial electrical resistance measurements indicating dysfunction in mutant pericytes. 2P confirmed significant leakage in mutants, which correlated histological findings that revealed structural abnormalities in the blood vessels. Future work includes studying the BBB integrity upon using a custom CRISPR-Cas9 adenine base editor delivered by an AAV construct as treatment for MSMDS.

POSTER NUMBER:
148

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Improving journal author guidance to address ethical challenges in the utilization of race and ethnicity population descriptors in human neuroscience research

Investigators: J. Gerold, L. Lang, C. McFarland, F. X. Shen

Addressing systemic exclusion practices and improving racial and ethnic diversity in neuroscience research has gained significant attention in recent years. It is recognized that more diverse participation improves the generalizability of research findings, identifies clinically relevant differences across sub-populations, and promotes health equity through increased access to research participation. While there is general agreement that more racial and ethnic diversity in neuroscience research participation is needed, there is less agreement on how the social constructs of race and ethnicity should be conceptualized, measured, and reported in neuroscience research publications.

As part of an NIH BRAIN-funded project, Recruitment, Engagement, and Access for Community Health Equity for BRAIN Next-Generation Human Neuroimaging Research and Beyond (REACH for BRAIN), we reviewed current policies for authors on reporting population descriptors in 25 leading neuroscience journals. From June 28, 2024, to July 10, 2024, we examined each journal's online author information text and reached out to the senior editors of each journal.

We found journals publishing human neuroscience research have few guidelines and little consistency between journals for authors on whether and how to report race and ethnicity population descriptors. To facilitate more representative participation and avoid repeating historical misuse of racial differences in brain research, we conclude that neuroscience journals should require reporting of race, ethnicity, or ancestry, or an explanation for why it is not reported. Specific guidance should be: (1) co-developed with community input; (2) aligned with federal reporting requirements; and (3) flexible to account for future changes in regulation and social conventions.

POSTER NUMBER:
149

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Modeling Brain State Dynamics in Older Adults: A Hidden Markov Model Approach

Investigators: N. Ghavamizadeh, T. Sitnikova, J. B. Beckmann

The brain's capacity for transitions between functional states may be disrupted with aging, contributing to debilitating diseases like Alzheimer's disease. New insights into the mechanisms behind these changes can come from innovative quantification of brain activity dynamics across various spatial and temporal scales. A Hidden Markov Model (HMM) approach can detect transient brain activity states and their alterations.

We applied HMM to resting-state functional magnetic resonance imaging (fMRI) data from 70 adults (55–85 years old, 35 females). Preprocessing was performed using FreeSurfer. HMM analysis was applied to 38 regions of interest defined by Yeo 2015 Brainmap Atlas. HMM inferred 12 distinct brain states that recurred over time.

We examined [1] how long the brain stayed in different functional states before transitioning out and [2] how irregular/jittered the progression from state to state was. Our findings suggest a shift in network engagement patterns with aging: visits to default mode network (DMN) states were prolonged, and visits to sensory-motor networks were shortened ($p<.04$. Additionally, neural burstiness quantified by $B = (s - m)/(s + m)$, where m is the mean and s is the standard deviation of dwell times in a network, declines with age ($p<0.01$), indicative of reduced neural flexibility.

These findings demonstrate the utility of HMM in capturing dynamic brain network mechanisms. Our results suggest dysregulation of naturally irregular transitions between spontaneous activations in different brain networks with aging. Future research integrating highly temporally-resolved electrophysiology with fMRI could uncover how aging-related changes in network dynamics relate to neurodegenerative disease.

POSTER NUMBER:
150

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Can subscales of the upper-limb Fugl-Meyer assessment provide evidence for competition between descending motor tracts after stroke?

Investigators: A. M. Hadjiosif, J. A. DiCarlo, D. J. Lin

Stroke often causes upper extremity motor impairments, including abnormal synergies —abnormal co-activation of muscles that limits the ability to individuate movement at different joints. A prominent model suggests abnormal synergies arise from competition between descending neural tracts that transmit motor commands to muscles. Specifically, stroke-related damage to the corticospinal tract (CST) is compensated by increased activity of the corticoreticulospinal tract (CRST) on the unlesioned side. However, CRST fibers connect to multiple different muscles, causing simultaneous activation and resulting in abnormal synergies. This model has not yet been directly demonstrated in stroke patients; doing so would reveal the CRST as a target for treatment.

Under this model, CRST overactivity would facilitate movement within abnormal synergies but impede movement that requires breaking out of these synergies. As evidence, recent work reported a negative relationship between stroke patients' scores on within-synergy vs. out-of-synergy subscales of the upper-limb Fugl-Meyer assessment (FMA). However, this analysis binned patients by total scores, potentially introducing spurious negative relationships. To investigate this potential issue, we analyzed FMA data from the Stroke Motor Rehabilitation and Recovery sTudy (SMaHRT, N=196). We found that the negative relationships detected by this type of analysis were similar to those detected using the same analysis in randomly permuted data, and thus likely spurious. Moreover, comparing longitudinal changes in these subscales suggests positive, rather than negative, correlations. Together, our analyses show no evidence of FMA sub-scores validating the competition model. Instead, more direct evidence might come from neurophysiological assessments of CST/CRST activity or interventions targeting CST/CRST outflow.

POSTER NUMBER:
151

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Dried blood spots as a matrix for measuring AD biomarkers: optimizing parameters of analysis and evaluating technical stability

Investigators: B. L. Hammerschlag, H. A. Fatima, J. Celedon, T. Ragas, H. A. Webster, S. E. Arnold, P. Kivisäkk, Massachusetts Alzheimer's Disease Research Center longitudinal cohort study

Background: Repeated biomarker measurements provide greater sensitivity for detecting within-person change, which in clinical trials can allow for reductions in sample sizes required to detect treatment effects and shorten trial periods. We validated Dried Blood Spots (DBS) as a novel matrix for measuring blood biomarkers of Alzheimer's disease (AD), as collection is easily repeatable, less burdensome and more economical than phlebotomy, and shipment and storage are simplified. Our goal was optimizing collection methods, measurement parameters, and evaluating the technical stability and day-to-day variability of repeat measurements.

Methods: We measured levels of phosphorylated tau 217 (pTau217) and glial fibrillary acidic protein (GFAP) using electrochemiluminescent immunoassays in DBS and paired plasma samples. Venous blood was obtained from participants in the Massachusetts Alzheimer's Disease Research Center's longitudinal cohort and patients undergoing diagnostic lumbar punctures at Massachusetts General Hospital. DBS samples were stored at room temperature and eluted at 37c for one hour.

Results: We optimized pre-analytical factors of DBS analysis by investigating differences in elution times, temperatures, and matrix and diluent effects. GFAP [median (IQR): 4.1 (6.7-2.2) pg/mL], and pTau217 [4.5 (5.6-3.3) pg/mL] were detected over the lower limit of quantitation in all samples. Excellent correlations between plasma and DBS concentrations were observed for GFAP ($r=0.90$; $p<0.0001$). Initial validation indicated acceptable correlations for pTau217 ($r=0.78$; $p<0.01$).

Conclusions: We found measurable levels of key biomarkers of AD in DBS samples. Concentrations were significantly correlated to levels in paired plasma. We are evaluating technical repeatability and variability in capillary DBS levels of pTau217 and GFAP.

POSTER NUMBER:
152

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Changes in Choroid Plexus Sub-Compartments in Aging and Premanifest Synucleinopathy Using High-Resolution 7 Tesla Structural and Functional MRI

Investigators: F. F. Hannanu, K. Singh, G. Garcia-Gomar, S. Grimaldi, S. Koley, A. Stefani, A. Videnovic, M. Bianciardi

The choroid plexus (ChP) is recognized for its roles in cerebrospinal fluid production, immune surveillance, and metabolic regulation within the central nervous system. While changes in total ChP volume with age are well established, the contributions of individual sub-compartments (stromal tissue, stromal vessels, and cysts) remain unclear. We manually segmented the ChP into sub-compartments in patients with isolated Rapid Eye Movement Sleep Behavior Disorder (iRBD), age-matched controls, and younger controls using high-resolution, multi-contrast, 7 Tesla MRI. We then assessed their volumes and the amplitude of resting-state functional signals, hypothesizing that morphological and functional alterations in these sub-compartments may be detectable in older adults and individuals with premanifest synucleinopathy.

Here we show a significant age-related increase in total ChP volume, driven by expansion of stromal tissue and stromal vessels, as well as increased functional signal amplitude, particularly in stromal tissue. In contrast, cyst volumes remained stable across all groups, suggesting that their formation is more closely tied to ChP histogenesis than to age-related degeneration. Our findings primarily reveal structural and functional changes in the ChP among older adults. The changes observed in iRBD may largely mirror typical aging rather than representing a distinct pathological signature. Additionally, investigating these sub-compartments may clarify whether targeted interventions could preserve ChP function, delay neurodegenerative processes, and support healthy aging. These results underscore the importance of detailed sub-compartment analysis of the ChP, enabled by high-resolution 7 Tesla MRI, to clarify its changes and offer valuable insights into its role in aging and neurodegeneration.

POSTER NUMBER:
153

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Locus coeruleus tau validates and informs high-resolution MRI in aging and at earliest Alzheimer's pathology stages

Investigators: A. T. Hary, S. Chadha, N. Mercaldo, E. C. Smith, A. Van der Kouwe, B. Fischl, C. Mount, L. Kozanno, M. P. Frosch, J. C. Augustinack

The accumulation of abnormally phosphorylated tau protein in the cerebral cortex is a landmark feature of Alzheimer's disease pathology. The locus coeruleus, a norepinephrinergic brainstem nucleus, has been identified as a site that develops tau pathology earlier than cortex. This early pathology has biomarker potential for Alzheimer's disease as it occurs before symptom onset, when treatments would be most effective. We sought to identify histological and anatomical changes that occur within the locus coeruleus during preclinical Alzheimer's disease stages through high-resolution postmortem MRI and validated tau histopathology in controls and the earliest Braak and Braak (BB) stages. Here we show significant locus coeruleus atrophy between BB 0 and II (30.0% smaller volumes, $p = 0.0381$) and patterns of subatrophy that affect the rostral-most part of the nucleus (49.2% smaller average volume, $p = 0.0381$). Histologically, we observed significant tau accumulation between BB I and II (37.6% increase, $p < 0.0001$), which may reflect a pathology change prior to presumptive cognitive impairment at BB III. Subregionally, tau accumulation occurred more severely in the middle third of the locus coeruleus. We also mapped our regionally specific and histopathology informed data onto high-resolution 3D MRI reconstructions of the same samples ($n = 11$). Taken together, our findings provide a novel assessment of locus coeruleus tau pathology during preclinical Alzheimer's disease stages, alongside spatial reconstructions that will serve as valuable references for in vivo locus coeruleus imaging.

POSTER NUMBER:
154

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Association between basal forebrain network connectivity and cognition in preclinical autosomal dominant Alzheimer's disease

Investigators: B. He, I. D. Palacio, P. O. Lopera, A. Espinosa, J. C. Becerra, L. Osorio , D. Alzate , S. Alvarez, V. Malotaux, C. Tristão-Pereira , M. Rowe, A. Giudicessi, S. D. Carmo, D. Aguillón, A. C. Cuello , Y. T. Quiroz

The cholinergic basal forebrain (BF), critical for attention, memory, and learning, shows altered functional connectivity in Alzheimer's disease. However, research in autosomal dominant AD (ADAD) is limited. We investigated BF functional connectivity and its cognitive associations in cognitively unimpaired PSEN1 E280A carriers from the world's largest ADAD cohort in Colombia.

This study included 127 cognitively unimpaired individuals from the PSEN1 Colombian kindred (60 carriers, 67 non-carriers; mean age: 30.67 ± 6.65 years, education: 12.24 ± 3.06 years), defined by Functional Assessment Staging (FAST) scores <2. All participants underwent resting-state fMRI and cognitive testing using the Mini-Mental State Examination (MMSE). Voxel-wise functional connectivity with basal forebrain regions was assessed using Pearson's correlation. Group differences were analyzed with two-sample t-tests controlling for age and sex, with cluster-wise correction via Monte Carlo simulations.

Carriers exhibited greater connectivity than non-carriers between the left nucleus basalis of Meynert and medial temporal lobe regions, which are linked to early tau accumulation and atrophy, as well as between the right nucleus basalis of Meynert and the salience network. Additionally, higher MMSE scores correlated with increased connectivity between the left nucleus basalis of Meynert and both the salience network and ventral striatum.

These findings suggest that basal forebrain connectivity with critical memory and attention regions is altered in cognitively unimpaired individuals with ADAD, underscoring the importance of further longitudinal studies and investigations with clinical populations to better understand its role in the onset and progression of cognitive decline.

Neurosciences

POSTER NUMBER:
155

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Lipidomic surveys in plasma reflect genotype and therapy dependent changes in striatum in a Huntington's disease mouse model

Investigators: A. Boudi, C. Seeley, E. Sapp, R. Miller, S. Liu, K. Chase, K. Shing, R. Batista, M. Sena-Esteves, N. Aronin, M. DiFiglia, K. Kegel-Gleason

Reducing the burden of mutant Huntingtin (mHTT) protein in brain cells is a strategy for treating Huntington's disease (HD). However, it is still unclear what pathological changes can be reproducibly reversed by mHTT lowering. We previously found that lipid changes that occur with HD progression could be prevented by attenuating HTT transcription of the mutant allele in a genetic mouse model (LacQ140) with inducible whole-body lowering. Here, we tested whether intrastriatal injection of a therapeutic capable of repressing the mutant HTT allele with expanded CAG can provide similar protection against lipid changes in HD mice (zQ175DN). Wild-type or zQ175DN mice were injected with AAV9 bearing a cDNA for a zinc finger protein which preferentially targets mutant HTT (ZFP-HTT) to repress transcription. Proteins of caudate-putamen lysates were analyzed using various biochemical methods. Lipid analyses of caudate-putamen and plasma were conducted by liquid chromatography and mass spectrometry (LC-MS). Somatic expansion index was assessed using capillary electrophoresis of PCR products. We found lowering mHTT levels by 43% for 4 months prevented decreases in total lipids, and numerous changes in lipids of caudate-putamen in zQ175DN mice. Analysis of plasma demonstrated total lipid increases and lipid changes in monogalactosyl monoacylglycerol (MGMG) and certain phosphatidylcholine species were reversed with the therapy. Our data support the idea that mHTT lowering can provide meaningful benefits and support brain health. Furthermore, our data demonstrate that analyzing lipid signatures of brain tissue and peripheral biofluids are valuable approaches for evaluating potential therapies in a preclinical model of HD.

POSTER NUMBER:
156

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Functional analysis of O-GlcNAc in sleep and circadian rhythm in Drosophila

Investigators: K. L. Jay, T. R. Mandigo, A. Svoysky, A. Q. Ye, N. C. LoRocco, C. M. Woo, J. A. Walker

Dysregulation of O-linked N-acetylglucosamine (O-GlcNAc) is linked to many disorders, including neurodegenerative conditions like Alzheimer's disease. O-GlcNAc is a dynamic post-translational modification involved in the regulation of diverse biological processes including protein activity, signaling, and stability. Homeostasis of O-GlcNAcylation is maintained by the writer O-GlcNAc transferase (OGT) and eraser O-GlcNAcase (OGA). Neurodegenerative diseases are associated with disruptions in sleep and circadian rhythm but the molecular contributions of O-GlcNAc in sleep and neurodegeneration remain unclear. To investigate the molecular basis for O-GlcNAc-dependent regulation of sleep and circadian rhythm, we undertook phenotypic and proteomic studies of Drosophila with neuronal knockdown of OGT and OGA. Here we show that upon knockdown of OGT, flies experience a shorter circadian rhythm, while knockdown of OGA leads to an increase in arrhythmic behavior. We then performed glycoproteomic analysis to map O-GlcNAcylation in fly neurons. Our proteomics results identify candidate proteins with O-GlcNAc-dependent roles in sleep regulation and circadian rhythm for further functional characterization. To assess the role of specific O-GlcNAcylated proteins in regulating sleep in the flies, we developed an approach using OGT/OGA fused-nanobodies directed to GFP for targeted modulation of O-GlcNAcylation of any protein bearing a GFP-tag. We prioritized hits from our glycoproteomics dataset implicated in sleep and generated GFP-tagged transgenics to functionally assess them. By modulating O-GlcNAcylation of these substrates in neurons, we are evaluating their associated neurobehavioral phenotypes. Overall, this work will identify candidate glycoproteins for investigation of sleep/circadian rhythm in disease and provide novel targets for pre-clinical trials to ameliorate neurodegenerative phenotypes.

POSTER NUMBER:
157

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Damage to rich-club organization is related to clinical, but not patient reported outcome measures in acute ischemic stroke

Investigators: A. Kasemsantitham, E. Lindgren, A. Crippen, L. Angeleri, N. S. Rost, M. D. Schirmer

Background: Damage to a select group of regions in the brain, known as the rich club, disproportionately causes cognitive and functional decline in acute ischemic stroke (AIS). Here, we compare its efficacy as a biomarker for modeling clinical and patient-reported outcomes.

Methods: AIS patients, confirmed on MRI, from the COAST (2017-2020) cohort were analyzed. Rich-club regions damaged by stroke were manually identified on clinical diffusion-weighted MRI and quantified as number of regions affected (NRC). Functional outcomes were measured by the NIHSS, mRS, and Barthel Stroke Index. Patient-reported outcome measures (PROMS) included global physical and mental health T-scores. Ordinal and linear regression analyses were performed with NRC, baseline NIHSS, age, sex, and risk factors including hypertension and diabetes mellitus.

Results: 143 patients were included with a median age of 65 (IQR 59 – 71) years (57% male). Baseline characteristics included hypertension (77%), diabetes mellitus (26%), and baseline NIHSS with a median score of 2 (IQR 1 – 5). Results showed that greater NRC increases the odds of higher stroke severity (OR: 1.96 [95% CI 1.55 – 2.48], p<0.001), mRS (OR: 1.48 [1.13 – 1.94], p=0.005) and Barthel Index scores (OR: 0.026 [0.0008 – 0.841], p=0.042), demonstrating worse outcomes. However, we did not observe an association with global patient reported outcome measures.

Conclusion: Damaged rich club regions may serve as a translational biomarker of clinical, but not for patient reported outcome measures. Further investigations involving other radiological markers and PROMs sub-scores are warranted to fully investigate their relationship with NRC.

POSTER NUMBER:
158

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Fibrin(ogen) accelerates inflammatory-mediated vascular remodeling in a mouse model of cerebral amyloid angiopathy

Investigators: M. V. Sanchez-Mico, K. Walsh, S. Bonney, S. Van Veluw, M. G. Kozberg

Cerebral amyloid angiopathy (CAA) is a small vessel disease in which amyloid-β (Aβ) accumulates in leptomeningeal and cortical blood vessels, leading to vessel dysfunction and rupture. Recent evidence suggests vascular remodeling at later stages of CAA, including inflammatory-mediated removal of Aβ from vessel wall, may contribute to vessel rupture. Our findings from human tissue suggest that fibrinogen deposition, indicative of blood-brain barrier leakage, is an early event in CAA pathophysiology and may initiate and/or contribute to immune-mediated disease progression. We hypothesize that fibrinogen deposition, shown to trigger neuroinflammation, significantly contributes to disease progression via local perivascular inflammation. Our aim is to examine the effects of fibrinogen deposition on the vasculature of aged APP23 mice (a model of CAA) using in-vivo multiphoton microscopy (MPM) and ex-vivo immunohistochemistry. 16-20 months old APP23 mice were equipped with a cranial window with a silicone port, intracortically injected with fluorescent human fibrinogen (n=9) or ACSF with Texas Red (n=8), repetitively imaged under MPM, then euthanized 1-4 weeks post-injection. At 1 week, ex-vivo, fibrin depositions were associated with microglial activation (2/2 FI vs. 0/2 ACSF-injected control mice). Injections near an arteriole correlated with local vascular Aβ removal in FI mice at 2-4 weeks (4/6 vs 0/5 ACSF). Preliminary assessments of immunostained vessels revealed local inflammation associated with vascular remodeling sites in FI mice. Our findings suggest that fibrin deposition leads to accelerated vascular remodeling (local Aβ removal) through perivascular inflammation. Therefore, fibrin(ogen) could be a therapeutic target to prevent vessel rupture in patients with late-stage CAA.

POSTER NUMBER:
159

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Assessing the Efficacy of The NIH Toolbox to Characterize Executive Functioning Deficits in Autistic Individuals

Investigators: G. K. Levine, R. M. Joseph, T. Kenet

Autism Spectrum Disorder (ASD) is a neurodevelopmental disorder often characterized by executive functioning challenges such as task completion, focus, and memory. A better understanding of this profile is crucial for improving support for individuals with ASD. While there are multiple standardized assessments available, there is no unifying standard. The NIH Toolbox Cognition Battery (NIHTB-CB) creates this- an iPad-administered, easily accessible set of standardized tests designed to simplify cross-labs standardization for participants. While its focus is not exclusive to executive function, the NIHTB-CB assesses three core domains- inhibitory control, working memory, and cognitive flexibility. Although previous work has suggested this tool consistently assesses executive function in children and adolescents with ASD, evidence is limited, and little research has compared the NIHTB-CB to other validated reports of executive function measures. In this study, we compared the effectiveness of the NIHTB-CB to assess executive function in individuals with ASD (n=50, ages 14-32) relative to age- and IQ-matched typically developing (TD) individuals (n=49), when compared to another standardized self-report assessment. Participants completed three executive function sub-tasks within the NIHTB-CB and the Behavior Rating Inventory of Executive Function questionnaire. In our cohort, the NIHTB-CB showed no significant differences in executive function measures between the ASD and TD groups, while the scores from the BRIEF showed highly significant differences across all categories. Our results suggest that there may differential sensitivity between the two approaches in capturing executive function profiles in individuals with ASD, with a tendency for NIHTB-CB lab-based tests to underestimate differences in this group.

POSTER NUMBER:
160

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Variability in Muscle Co-activation Patterns Within Upper Extremity Fugl-Meyer Sub-Scores After Stroke

Investigators: A. Y. Lin, S. K. Cavanagh, C. Finetto, F. Tessari, K. C. Rishe, M. Woodbury, S. Kautz, D. J. Lin

Background: In able-bodied individuals, functional task performance depends on coordinated upper extremity (UE) muscle activation. After stroke, damage to descending motor tracts disrupts muscle coordination, leading to abnormal synergies (impaired muscle co-activation patterns). Clinical measures like the Fugl-Meyer Assessment (FMA) are based on clinical observation and do not directly assess these patterns. More precise approaches to quantify abnormal co-activation patterns post-stroke are needed.

Objective: This study characterized abnormal muscle co-activation patterns with EMG. We examined whether individuals with the same clinical FMA sub-scores exhibit similar or distinct muscle co-activation patterns.

Methods: Ninety-two chronic stroke subjects (FMA range: 10-60, no reflexes measured) performed an in-synergy (FMA Flexor Synergy) and out-of-synergy task (FMA Shoulder Flexion to 180). EMG from seven UE muscles was recorded bilaterally. EMG was decomposed into modules using non-negative matrix factorization. Subjects were stratified by their FMA item scores. Pairwise co-activation similarity distributions within score groups were obtained and compared to a reference using a t-test.

Results: For in-synergy, middle-score group (moderately-impaired) subjects exhibited similar co-activations ($p = 0.011$), while high-score group (least-impaired) subjects showed significantly different co-activations ($p < 0.001$). For out-of-synergy, low-score group (most-impaired) subjects had significantly similar co-activations ($p < 0.001$), while middle-score group subjects had significantly different co-activations ($p < 0.001$).

Conclusion: In severely impaired individuals, clinical observation via FMA captures muscle co-activation patterns, but for those with milder impairment, EMG-based analysis is necessary to discern phenotypic differences. These findings highlight EMG as a supplemental tool to clinical observation-based assessment of abnormal muscle co-activation post-stroke.

POSTER NUMBER:
161

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Impact of Modifiable Risk Factors on Neuroimaging Markers of Brain Health in Acute Ischemic Stroke

Investigators: E. Lindgren, L. Angeleri, A. Crippen, A. Kasemsantitham, N. S. Rost, M. D. Schirmer, GASROS

Background: Preserved brain health is related to more favorable outcome after acute ischemic stroke (AIS). However, the association between modifiable risk factors and neuroimaging markers of brain health in AIS has not been investigated.

Methods: We analyzed AIS patients with available admission MRI from the GASROS (2003-2011) cohort. White matter hyperintensity (WMH) and brain volumes were automatically assessed based on T2-FLAIR. We quantified brain health using effective reserve (eR), defined as a latent variable in structural equation modeling based on age, WMH, and brain volume. The association between modifiable risk factors (hypertension, diabetes mellitus type 2, body mass index (BMI), estimated glomerular filtration rate (eGFR), history of smoking) and brain health were assessed using multivariate regression, adjusting for age and sex.

Results: We included 557 patients (median age 66 [IQR 55-76], 35% female) in our analysis. Baseline characteristics included diabetes (20%), hypertension (62%), history of smoking (65%), BMI median 27 (IQR 24-30) and NIHSS median 2 (IQR 1-6). At 90-days 24% of patients had modified Rankin Scale 3-6. In multivariable analysis (aOR [95% confidence interval]; p-value) diabetes (0.91 [0.86-0.97]; 0.004), hypertension (0.94 [0.89-0.99]; 0.021), lower eGFR (1.01 [1.00-1.02]; 0.046), higher age (0.67 [0.66-0.68]; <0.001) and female sex (0.73 [0.68 - 0.78]; 0.001) were associated with lower brain health at admission.

Conclusions: Modifiable risk factors are associated with neuroimaging markers of brain health at admission in patients with acute ischemic stroke. Longitudinal studies exploring these risk factors as potential treatment targets to improve brain health and outcome after stroke are warranted.

POSTER NUMBER:
162

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A novel brain-permeable HDAC11-selective inhibitor significantly reduces AD neuropathology in a Tau P301S mouse model.

Investigators: F. Lobo, Y. Liu, P. Bai, L. Yang, A. Gomm, S. Shen, B. Zhang, R. Tanzi, C. Wang, C. Zhang

Background: Alzheimer's disease (AD) is a neurodegenerative disorder and is the most common form of dementia. Although the understanding of AD has been greatly improved through decades of research, an effective therapy that can stop or reverse AD has not yet been developed. Histone deacetylase (HDAC) activity and expression are implicated in cognitive decline and neuroinflammation in Alzheimer's disease (AD). This strongly suggests that HDAC inhibition is a promising lead towards developing improved treatment for AD. The epigenetic protein histone deacetylase 11 (HDAC11), an important regulator of immune regulation and other cellular processes, is one of the potential therapeutic targets for AD. Here, we investigated the role of an HDAC11 inhibitor (PB151) for the treatment of AD.

Methods: In this work, PB151 was developed through structural based rational design. PB151 has high selectivity against HDAC11 and is safe and feasible to administer in mice. We treated 8-month-old female Tau P301S mice for 2 months with PB151 and studied its effects on cognition, Tau neuropathology and neuroinflammation using mouse behavior tests, western blots, immunohistochemistry, MSD, and RNA sequencing.

Results: Here we show, in Tau mice treated with PB151 compared to Vehicle, we observed a significant improvement in cognition, reduction in phosphorylated Tau protein levels, modulation in the levels of microglia and an alteration of gene expression in multiple pathways related to neuroprotection, serine metabolism and synaptic plasticity.

Conclusions: Our findings reveal that HDAC11 is a novel drug target for AD and Tauopathies and PB151 is a potential therapeutic for late-stage AD.

POSTER NUMBER:
163

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Neuroinflammation in the Primary Somatosensory Area is associated with Pain Widespreadness in Individuals with Chronic Low Back Pain

Investigators: E. Luo, J. Murphy, M. Kim, A. Axelrod, M. Mohammadian, D. Ellingsen, J. Cooper-Hohn, C. Pike, N. Mercaldo, Y. Zhang, A. Evins, R. Edwards, V. Napadow, J. Gilman, M. Loggia

Our laboratory has shown that patients with chronic pain conditions, including chronic low back pain (cLBP), demonstrate elevated 18 kDa translocator protein (TSPO) positron emission tomography (PET) signal, a putative marker of neuroinflammation. Here, we explored the association between neuroinflammation in the primary somatosensory cortex, which contains the somatosensory representation of the entire body, and clinical presentation of cLBP. Specifically, we hypothesized that increased neuroinflammation in the post-central gyrus (PCG) would be correlated with increased pain widespreadness in the lower back. Using integrated 3T positron emission tomography/magnetic resonance imaging and the TSPO PET radioligand [11C]PBR28, we scanned 40 patients. Using digital pain drawings that dynamically captured patients' cLBP symptoms (Neubert et al., et al 2018), we computed the widespreadness of each patient's clinical pain symptoms within the back area. In region-of-interest analyses, we found that the average Standardized Uptake Value Ratio (SUVR) extracted within the PCG label from the Harvard Oxford Cortical Atlas (threshold=30) significantly predicted increased lower back pain widespreadness ($r=.33$; $p<.03$). Additionally, voxelwise analyses using the same label as the pre-threshold mask (FSL FEAT OLS, voxel-corrected using a voxel P threshold of $p<.05$) revealed a significant cluster in the PCG area, lateralized to the left hemisphere (peak z-stat: $x=64$; $y=52$; $z=58$). Overall, here we show that there is an association between neuroinflammation and a clinical symptom (i.e., pain widespreadness) in cLBP, highlighting the clinical significance of TSPO signal elevation observed in chronic pain.

POSTER NUMBER:
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Distinct early cortical thickness patterns in heterozygous APOE3-Christchurch carriers and age-matched controls

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Background: The APOE3-Christchurch (APOE3Ch) variant has been linked to protection against Alzheimer's disease (AD), even in individuals with significant genetic and pathological risks. We analyzed cortical thickness (CT) in middle-aged heterozygous APOE3Ch carriers compared to age-matched non-carrier family members to explore potential early structural brain differences associated with this protective effect.

Methods: We studied 52 non-demented individuals (MMSE ≥24), including 15 APOE3Ch carriers (aged 40.2±12.4 years, 53% female) and 37 non-carriers (aged 40.7±5.6 years, 54% female), all undergoing structural MRI. We first used voxel-based morphometry analyses adjusted for age to assess cortical differences. Subsequently, CT across 68 ROIs (Desikan-Killiany atlas) and an AD-related meta-ROI were compared using multiple linear regression adjusted for age. Clinical measures included MMSE and Functional Assessment Staging Tool (FAST) scores.

Results: Heterozygous APOE3Ch carriers had similar MMSE and FAST scores to non-carriers (mean MMSE: APOE3Ch carriers=28.40±0.99, non-carriers=28.76±1.14, p=.27; mean FAST: APOE3Ch carriers=1.4±0.63, non-carriers=1.05±0.23, p=.06). Both groups had similar sex distribution (χ^2=0.002, p=.96), though APOE3Ch carriers reported fewer years of education (mean: APOE3Ch carriers=8.33±3.99 years, non-carriers=12.24±3.66 years, p=.003). Whole-brain voxel-wise and ROI analyses revealed increased fronto-parietal CT in APOE3Ch carriers, alongside reduced thickness in occipital and temporal regions. Cortical thickness within the AD-related meta-ROI was comparable between APOE3Ch carriers and non-carriers (mean CT: APOE3Ch carriers=2.50±0.07mm, non-carriers=2.47±0.10mm, p=.23).

Conclusion: These findings suggest distinct CT patterns in APOE3Ch carriers, with fronto-parietal thickening potentially linked to cognitive reserve and AD resistance. Future multimodal imaging studies are needed to further elucidate the mechanisms underlying the protective effects of the APOE3Ch variant.

Neurosciences

POSTER NUMBER:
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Transcriptomic Signatures of ASD Risk Genes Uncover Molecular Convergence in Idiopathic Autism

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Autism spectrum disorder (ASD) is a neurodevelopmental condition characterized by impairments in social communication, interaction, and repetitive behaviors. It is classified into syndromic ASD (sASD), associated with known genetic abnormalities, and idiopathic ASD (iASD), whose etiology remains largely unknown despite consistent transcriptomic dysregulations in the cerebral cortex. To investigate ASD risk genes, we introduce TARGAN (Transcriptomic Atlas of ASD Risk Genes in Non-syndromic Autism), a publicly accessible database for analyzing transcriptomic signatures in postmortem cerebral cortex samples from iASD and neurotypical controls. By integrating transcriptome data from iASD and Dup15q sASD postmortem brain tissues with induced pluripotent stem cell (iPSC) models of two ASD subtypes—autistic individuals with average brain size (ASD-N) and those with disproportionate megalencephaly (ASD-DM)—we examine transcriptomic alterations in ASD risk genes and their roles in ASD pathology. Our analysis reveals widespread transcriptomic dysregulations, especially in the visual and auditory cortices, with pronounced changes in severe ASD forms such as Dup15q syndrome and ASD-DM. These dysregulations affect neuronal and synaptic genes and alter cell-specific expression in inhibitory and excitatory neurons, astrocytes, and microglia. We identify SOX5 as a key perturbed transcription factor, suggesting convergent molecular mechanisms across genetically diverse ASD cases. Our findings highlight the polygenic effects of ASD risk genes in shaping molecular pathologies in iASD. TARGAN serves as a valuable resource for further exploration of these complex molecular landscapes, particularly in idiopathic ASD, advancing our understanding of ASD pathophysiology.

POSTER NUMBER:
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Drosophila modeling of insomnia- and cardiovascular disease-associated genes finds excessive sleep correlates with aberrant cardiac function

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Insomnia disorder occurs in 10-20% of the population and is an important risk factor for incident cardiovascular disease (CVD) conferring a >2-fold increased causal risk. However, the underlying pathways and mechanisms linking the two remain poorly understood. We utilized the recent advances in large-scale sleep GWAS to identify human genes on haplotypes associated with insomnia and other sleep traits. From these candidate loci, we prioritized those with only one or two genes located within the haplotype and/or, with prior evidence of links to CVD, coronary artery disease (CAD), or cardiometabolic disease (CMD). After identifying Drosophila orthologs of these candidate genes, we used RNAi to knock down expression of each ortholog in neurons or the heart to assess their cell-autonomous effects on sleep and cardiac function respectively. Since mendelian randomization studies in humans have found insomnia symptoms causally contribute to CAD, we also looked at cell non-autonomous effects of neuronal KD on cardiac function and heart KD on sleep. Our cell non-autonomous experiments uncovered a strong association between excessive sleep and aberrant cardiac function. These cell non-autonomous experiments highlight various pathways that are essential for the functions of both tissues as well as potential pathways conferring cell non-autonomous regulation of sleep and cardiac function, providing a shortlist of therapeutically relevant genes and pathways that link insomnia, sleep and CVD.

Neurosciences

POSTER NUMBER:
167

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Unraveling the inflammatory landscape in X-linked dystonia parkinsonism

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We have recently demonstrated an increase in astrogliosis and microgliosis in human post-mortem prefrontal cortex (PFC) derived from people who lived with X-linked Dystonia Parkinsonism (XDP), a neurodegenerative disorder endemic in the Philippines, suggesting a role for neuroinflammation in disease pathogenesis. We also reported an increase in levels and activity of myeloperoxidase (MPO), an enzyme mainly released by neutrophils and macrophages; however, several evidence suggest that it can also be released by glial cells. Here, we used a panel of 10 antibodies (GFAP, CD68, MMP9, CD3, CD45, CD163, CD4, CD8, neutrophil elastase, and Ki67) for imaging mass cytometry studies to characterize the inflammatory landscape in XDP and determine the source of MPO. Specifically, we measured protein levels and localization in PFC from people who lived with XDP, cerebrovascular disease (CVD), or Huntington's disease (HD), as well as non-neurological control PFC. Our results revealed that while there were no changes in the levels of nine proteins between groups, there was a decrease in MMP9 levels in XDP PFC compared to controls. Additionally, our correlation revealed an impact of GFAP on age at disease onset and age at death, further supporting a role for astrogliosis in XDP.

POSTER NUMBER:
168

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Neuroinflammation alters neuronal activity in an experimental model of multiple sclerosis

Investigators: W. H. Ndambakuwa, R. L. Gillani, B. J. Bacskai, M. Algamal, E. N. Kironde, S. Whiteman

Background: Multiple sclerosis (MS) is an autoimmune disease where neuroinflammation damages the protective myelin sheath around nerve fibers, leading to demyelination within the brain and the spinal cord. Demyelination contributes to physical disability and cognitive impairment in people living with MS (PwMS). Beyond demyelination, dysfunction and loss of neurons and synapses occur in MS. This dysfunction is also a major driver of physical and cognitive dysfunction in PwMS. There are currently no effective treatments for neuroprotection and restoration, making it crucial to develop therapies that protect and repair neuronal function. In our previous research, we found that neuroinflammation disrupts excitatory synapses in the experimental autoimmune encephalomyelitis (EAE) model. We hypothesized that neuronal and synaptic dysfunction caused by neuroinflammation alters neuronal activity.

Methods: We injected an AAV vector into the brains of mice to express a fluorescent calcium indicator, GCAMP7s. Longitudinal multiphoton neuronal calcium imaging was carried out through an implanted cranial window to monitor neuronal activity during the clinical course of EAE. Clinical scores were used to monitor motor weakness during EAE development.

Results: We discovered that neurons exhibit sustained hypoactivity in the setting of neuroinflammation. In some mice, we found that neuronal hypoactivity began before the development of clinical EAE symptoms.

Discussion/ Future directions: This study unravels the pathophysiology of neuronal dysfunction caused by neuroinflammation. In the future, we plan on testing therapies that protect against altered neuronal activity in the setting of neuroinflammation. We anticipate that discoveries from these experiments will aid in the development of neuroprotective treatments.

POSTER NUMBER:
169

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Impact of Lifetime Estradiol Exposure on Memory Function in Midlife Women

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Higher peripheral endogenous estradiol concentration and supplemental exogenous estradiol have been associated with improved memory performance in women post-menopause. We investigated the impact of lifetime cumulative exposure to endogenous and exogenous estradiol on cognitive performance in women in midlife.

Participants (66F) completed cognitive testing at two time points 8 years apart. Lifetime estradiol exposure (LEE) was calculated at Time 2 using a standardized score of reproductive years plus use of oral contraceptives (OC) and hormone therapy (HT) in one's lifetime. LEE was assessed in relation to cognitive performance at Time 2 and change in performance from Time 1 to Time 2 using generalized estimating equation-based linear models.

Higher LEE was significantly associated with better working (β=3.63, p=0.0004) and verbal (β=0.38, p=0.05) memory performance and less decline in working (β=2.52, p=0.02) and verbal (β=0.50, p=0.004) memory performance over time. Greater reproductive years was significantly associated with better working memory (β=0.47, p=0.01) and less decline in verbal memory (β=0.09, p=0.009). OC use was significantly associated with better working memory (β=8.73, p=0.02). HT use was significantly associated with less decline in working (β=4.13, p=0.03) and associative (β=2.88, p=0.03) memory over time.

LEE is associated with higher working and verbal memory performance in midlife and less decline in working, verbal, and associative memory over time. Number of reproductive years contributed most significantly to the predictive power of LEE. Results suggest that higher LEE, by endogenous and exogenous means, may slow cognitive decline in midlife women and contribute to maintaining intact memory function with aging.

POSTER NUMBER:
170

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Blocking RAN translation without altering repeat RNAs rescues C9ORF72- related ALS/FTD phenotypes

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Expanded G4C2 repeats in an intron of C9ORF72 represent the most common genetic cause of frontotemporal dementia (FTD) and amyotrophic lateral sclerosis (ALS). Three primary mechanisms have been proposed to contribute to disease pathogenesis: C9ORF72 protein haploinsufficiency, the accumulation of toxic repeat containing RNAs transcribed from both sense and antisense strands, and the translation of these repeats into dipeptide repeat proteins (DPRs). The relative contributions of these mechanisms remain a topic of debate in the field as disentangling their individual contributions has been challenging. To specifically assess the role of DPRs, we introduced a point mutation (CUG>CCG) in a key upstream CUG codon required for initiating DPR translation. This mutation did not impact the formation of repeat RNA. However, DPR expression, including poly-GA, poly-GP, and poly-GR, was significantly reduced. In the present study, we show that suppressing DPR expression resulted in the mitigation of behavioral deficits and neuropathological abnormalities in C9ORF72 mouse models and patient-derived neurons. Notably, key disease phenotypes, such as neuroinflammation, phosphorylated TDP-43 inclusions, elevated neurofilament levels, and motor neuron degeneration, were alleviated. Furthermore, the CUG>CCG mutation significantly improved the survival of induced pluripotent stem cell (iPSC)-derived neurons from C9ORF72 ALS/FTD patients, emphasizing the direct toxicity of DPRs. We further demonstrate that sense poly-GP and poly-GR production occurs via frameshifting in vivo and in patient neurons, highlighting the importance of translational context. These findings suggest that targeting DPR production, rather than repeat RNA accumulation alone, may offer a more effective therapeutic approach for C9ORF72-associated neurodegeneration.

POSTER NUMBER:
171

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Genetic and pharmacological inhibition of PKC alleviates nucleocytoplasmic transport disruption in FUS-mediated ALS

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Impaired nucleocytoplasmic transport has emerged as a central disease mechanism in several neurodegenerative disorders. Mutations in the RNA-binding protein FUS is linked to severe forms of ALS, including juvenile ALS, and leads to cytoplasmic mislocalization and aggregation of nuclear FUS protein. We observe that patient-derived cells harboring FUS mutations exhibit abnormal nuclear morphology and cytoplasmic mislocalization of several nuclear membrane components, including nucleoporins and Lamin B1. Through a phenotypic small-molecule screen, we identified protein kinase C (PKC) inhibitors as potent rescuers of FUS mislocalization and nuclear membrane defects. We demonstrate that PKC is abnormally activated in patient-derived cells with FUS-ALS mutations, and that either genetic or pharmacologic inhibition of PKC alleviated FUS-related phenotypes across patient fibroblasts, iPSC-derived motor neurons and Drosophila models. This study provides evidence that mutations in FUS impairs nucleocytoplasmic transport by sequestering central components of the nuclear membrane and establishes PKC inhibition as a potential therapeutic approach for FUS-mediated ALS.

Neurosciences

POSTER NUMBER:
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X-linked dystonia-parkinsonism is a novel genetic four-repeat tau astrogliopathy

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X-linked dystonia-parkinsonism (XDP) is a rare neurodegenerative disease caused by a non-coding, SINE-VNTR-Alu (SVA) retrotransposon-associated hexanucleotide repeat expansion in the TAF1 gene. Prior investigations have revealed marked striatal atrophy, reduced cortical thickness, and gray matter pathology in the cerebellum. However, the pathogenic mechanisms driving neurodegeneration and biomarkers reflecting these processes remain elusive. Here, we report a pathogenic imbalance of tau isoforms and the aggregation of hyperphosphorylated, four-repeat tau in the brains of patients with XDP. Neurotoxic tau oligomers accumulated predominantly in striatal astrocytes and were significantly associated with repeat length and age at disease onset. Transcriptomics revealed dysregulation of pathways previously implicated as modulators of tau aggregation in the XDP striatum, including mitochondrial dysfunction and the ubiquitin-proteasome system. Furthermore, plasma phosphorylated tau181 (p-tau181) and glial fibrillary acidic protein (GFAP), a marker of astrocyte reactivity, discriminated XDP cases from controls with similar efficacy as neurofilament light chain (NfL), a biomarker of neuronal damage. Our findings converge on defective tau proteostasis as a central disease mechanism in XDP, uncover opportunities for testing tau-lowering strategies as potential treatments for this movement disorder, and provide a roadmap for therapeutic and biomarker discovery for rare neurodegenerative diseases in isolated populations.

POSTER NUMBER:
173

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Lipid droplet dynamics in Huntington's Disease

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A high load of lipofuscin juxtaposed to lipid droplets (LDs) has been described in brains of patients with Huntington's disease, a fatal neurodegenerative disorder. Neutral lipids normally are stored in LDs in astrocytes and can be transported out of LDs and delivered to the mitochondria for metabolism by beta-oxidation. Using double-label immunofluorescence we demonstrated that LDs are present in astrocytes and microglia, but significantly increased in neurons in striatum of aged Q175 HD mice compared to WT mice. One hypothesis is that LD dynamics are altered in the presence of mutant Huntingtin, preventing efficient extraction/recovery of lipids stored in LDs for efflux from cells. We tested whether LD formation or recruitment of stored lipids were changed upon lipid loading and starvation in human IPSC derived cortical neuronal cultures from a human control versus HD 109Q cells. LDs accumulated in both astrocytes and neurons after loading with oleic acid detected with a fluorescent Bodipy-C12 tracer. Changes in LD features were observed between control and HD109 neuron-like cells. With starvation, neuron-like cells in HD IPSC cultures had fewer LDs compared to the unstarved, lipid-loaded cells, but LD size was significantly larger. In addition, HD neurons had significantly more LDs compared WT neurons in both lipid-loaded and starved conditions. Glia cells present in the neuronal cultures also accumulated LDs and showed similar changes between control and HD109Q. These data suggest altered LD dynamics in human HD cells might contribute to energy deficits in HD.

POSTER NUMBER:
174

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Arteriolosclerosis in Patients with Cerebral Amyloid Angiopathy - an MRI and Histopathological Study

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Background: Cerebral Amyloid Angiopathy (CAA), characterized by amyloid-β accumulation in leptomeningeal and cortical vessels, is a leading cause of intracerebral hemorrhage (ICH) lacking effective treatment options. White matter (WM) lesions like subcortical enlarged perivascular spaces (ePVS) often precede hemorrhagic lesions in CAA and are linked to cognitive decline. Arteriolosclerosis of the subcortical WM is common in CAA, but its role in WM injury in CAA is understudied. This study aims to explore arteriolosclerosis in CAA using MRI and histopathology.

Methods: ARTS, an automated in-vivo classifier of arteriolosclerosis was applied to 3T MRI-scans (T1-w, FLAIR and DTI) of 40 patients with CAA and 6 controls (72.5±8.4y, 18F). Subcortical ePVS were counted on T2-w MRI, and CAA severity was assessed with a composite CAA score. For the autopsy study, 19 cases (74.1±8.2y, 7F) with a diagnosis of definite CAA upon histological examination were included. Arteriolosclerosis and ePVS % area was assessed on Hematoxylin & Eosin stained sections in the subcortical WM.

Results: ARTS Score was higher in probable CAA patients compared to controls (Mdn CAA= –0.042, Mdn CTRL= –0.289, U=35, $p<0.01$). ARTS and CAA Scores were positively correlated in the CAA group ($\rho=0.40$, $p<0.05$). ARTS Score was a predictor of subcortical ePVS count (linear regression analysis, $\beta=34.3$, $R2=0.10$, $p<0.05$). On histopathology, arteriolosclerosis severity was associated with ePVS %area (linear mixed effects model, est.=0.243, $R2=0.57$, $p<0.005$).

Conclusions: Arteriolosclerosis is associated with WM injury in CAA. Our findings highlight the possible pathophysiological overlap of both pathologies. More subjects will be added to the analysis.

Neurosciences

POSTER NUMBER:
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Elevated TDP-43 serum levels associated with postoperative delirium following major cardiac surgery

Investigators: C. Simon, O. K. Graves, O. Akeju, T. B. McKay

Postoperative delirium is a recurring complication among vulnerable patients undergoing major cardiac surgery. While delirium has been associated with prodromal dementia, there is minimal evidence to support the causality of this nuanced relationship. Clarification as to how postoperative delirium might lead to neurodegenerative dementias, perhaps through evidence of contemporaneous biomarkers, would heighten the plausibility of a causal correlation. TAR DNA-binding protein 43 (TDP-43), a nuclear protein essential for transcriptional events, has been linked to pathological aggregation in Alzheimer's disease-related dementias (ADRD). Circulating TDP-43 levels in cardiac surgical patients aged 60 years and older were evaluated in a biobank derived from the Minimizing ICU Neurological Dysfunction with Dexmedetomidine-induced Sleep (MINDDS) clinical trial. Serum total TDP-43 levels, measured with a single molecule array (Simoa), were compared across preoperative and postoperative day one timepoints according to delirium status assessed using the Confusion Assessment Method (CAM). Total serum TDP-43 levels increased by 16.5% (95% CI: 5.9% to 27.9%, p = 0.0021) on postoperative day one compared to baseline levels. This increase was more pronounced in patients who experienced delirium (median increase of 55.1%, 95% CI: 22.9% to 96.4%, p = 0.0002). In the validation cohort, TDP-43 levels were found to be significantly elevated immediately following cardiopulmonary bypass, with a gradual decrease by postoperative day one. Our findings demonstrate that post-cardiac surgery delirium among vulnerable patients is associated with significant elevations in circulating TDP-43. This relationship suggests that TDP-43 may serve as a biomarker for acute neurological insults and blood-brain barrier integrity following cardiac surgery.

POSTER NUMBER:
176

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Identifying Tau proteopathic species isolated from Alzheimer's disease brains

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Aggregation of the protein Tau is a hallmark of Alzheimer's disease (AD) and other neurodegenerative diseases termed 'Tauopathies'. The largest Tau aggregates in AD, known as neurofibrillary tangles (NFTs), have well-defined structures and abnormal post-translational modifications (PTMs). These large, insoluble, Tau aggregates are generally thought to be the main neurotoxic and clinically relevant Tau species. However, there is growing evidence to suggest that high-molecular-weight (HMW) soluble Tau oligomers play a key role in toxicity and proteopathic function. Though HMW Tau is known to be able to induce aggregation, it is unclear what specific tau species exist within the HMW tau population. Utilizing anion exchange chromatography (AIEX), HMW tau from 9 AD brain extracts was fractionated based on the net charge of Tau species. The bioactivity of this fractionated tau was evaluated using a well-established Forster resonance energy transfer (FRET) biosensor cell line. Across all nine cases, HMW Tau eluting earlier in AIEX showed virtually no bioactivity, while later-eluting species were bioactive. This suggests that the HMW Tau population consists of both 'non-bioactive' and 'bioactive' subspecies, with the latter being more heavily modified and negatively charged. Through various microscopy techniques (super-resolution microscopy, atomic force microscopy, and immunogold transmission electron microscopy) we confirm that both 'bioactive' and 'non-bioactive' HMW tau are oligomeric and non-fibrillar. To follow up on this work we hope to characterize differences in the PTM profile and structure of these two populations of oligomeric Tau utilizing mass spectrometry and cryogenic electron microscopy, respectively.

POSTER NUMBER:
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Hippocampal ripples predict motor learning during brief rest breaks in humans

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Procedural memory is classically thought to not involve the hippocampus, but recent findings challenge this view. Here we provide direct human evidence for a mechanism in a role of the hippocampus in procedural memory, specifically in offline motor learning.

Critical aspects of motor learning and memory happen offline, during both wake and sleep. When healthy young people learn a motor sequence task, most of their performance improvement happens not while typing, but offline, during interleaved rest breaks. In contrast, the performance of patients with dense amnesia due to hippocampal damage gets worse over the rest breaks and improves while typing. These findings indicate that an intact hippocampus is necessary for offline motor learning during wake, but do not specify its mechanism. Here, we studied epilepsy patients (n=17) undergoing direct intracranial EEG monitoring of the hippocampus as they learned the same motor sequence task. Like healthy young people, they showed greater speed gains across rest breaks than while typing. They also showed higher hippocampal ripple rates during these rest breaks that predicted offline gains in speed. This suggests that motor learning during brief rest breaks during wake is mediated by hippocampal ripples.

Here we show direct evidence in humans that learning during offline waking states is mediated by ripples - a human corollary to existing rodent work. We provide a mechanistic explanation for previous findings from human neuroimaging studies of hippocampal memory evolution, and we extend our understanding of the role of hippocampal ripples beyond declarative memory.

POSTER NUMBER:
178

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Microglial Estrogen Receptors Program Male-Biased Vulnerabilities to Perinatal Challenges

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There is a strong male bias in the prevalence of many early onset neurodevelopmental disorders (NDDs). However, the mechanisms driving these sex biases remain elusive. Infections during the perinatal period are associated with increased risk of NDDs. Here, we use a mouse model of early-life immune activation via bacterial endotoxin infection that induces social behavioral deficits only in male mice and demonstrate that these behavioral alterations are dependent upon immune signaling of microglia, the resident innate immune cells of the brain. We show that these male-biased behavioral alterations are coupled to alterations in mitochondrial morphology, gene expression, and function specifically within microglia. Excitingly, through manipulation of developmental gonadal hormone levels, we demonstrate that this behavioral and cellular vulnerability to early-life immune activation is programmed by the male-typical perinatal gonadal hormone surge. Our overarching hypothesis is that gonadal hormones present during perinatal brain organization result in distinct sex-specific microglial and mitochondrial phenotypes, thereby increasing male vulnerability to early-life challenges. We are currently testing the hypothesis that perinatal gonadal hormones induce this sex-specific vulnerability to perinatal immune challenge through specific microglial estrogen receptors. To do so, we have created microglial conditional knockout mice that lack the G protein coupled estrogen receptor 1 (GPER1) or estrogen receptor alpha (ESR1) on microglia and are assessing social behavioral, neuroimmune, and microglial mitochondrial functional alterations in response to perinatal immune challenge in both female and male mice. Our preliminary results suggest that ESR1 signaling in male microglia programs this male perinatal vulnerability.

POSTER NUMBER:
179

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Parafoveal macular thinning and Alzheimer's disease risk in healthy midlife adults dependent on sex

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In Alzheimer's disease (AD), macular thickness is significantly thinner compared to healthy controls and is also related to worse cognitive performance. Here, we investigated macular thickness in 61 healthy adults (39M:22F; ages 50-70) at high risk (HR) (at least one APOE4 allele and a clinical risk factor of hypertension (HYP), type 2 diabetes (T2D), and/or depression (DEP)) or low risk (LR) (none) for AD, in relation to memory performance and amyloid (Aβ) pathology.

We assessed macular thickness using non-invasive Optical Coherence Tomography. Associative memory was measured by the Face-Name task. Aβ was detected with PET C-11PiB. Macular thickness was assessed in relation to memory performance and Aβ using general linear models adjusted for age.

Higher AD risk related to inner macular subfield thinning (β=-3.32, p=0.04), which, in turn, related to poor associative memory performance (β=0.02, p=0.01). In HR women, central subfield thinning related to greater Aβ pathology (β=-0.002, p=0.04). Sex-dependent effects were dependent on clinical risk factor, whereby T2D and HbA1c levels were associated with inner thinning (T2D: β=-9.79, p=0.02; HbA1c: β=-20.62, p=0.03), primarily in men (T2D: β=-28.55, p=0.04; HbA1c: β=-61.50, p=0.03). In contrast, HYP (β=-10.21, p=0.06), blood pressure (β=-0.61, p=0.03) and DEP (β=-13.36, p=0.03) related to inner subfield thinning in women.

In healthy midlife adults, macular thinning was associated with AD risk, Aβ pathology, and memory performance, with sex-dependent effects. Results suggest that non-invasive assessment of retinal changes may be used in risk-assessment to improve early detection and prevention before the onset of overt clinical symptoms.

Neurosciences

POSTER NUMBER:
180

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Association among cerebral glucose metabolism, mild behavioral impairment and cognition in autosomal-dominant Alzheimer's disease

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Neuropsychiatric symptoms, affecting 60%-90% of dementia patients, are increasingly recognized early manifestations of disease. Mild behavioral impairment (MBI) is an emerging construct characterized by decreased motivation and affective dysregulation in non-demented individuals that has shown inconsistent associations with neurodegeneration. This study investigates the relationship between MBI and cerebral glucose metabolism, a marker of synaptic dysfunction, in autosomal-dominant Alzheimer's disease (AD). We included 22 Presenilin-1 E280A mutation carriers (40.2±6.9 years) and 26 non-carriers (38.4±5.7 years) who completed the self-reported MBI-Checklist (MBI-C). They were classified as MBI- (MBI-C=0) and MBI+ (MBI-C>0). Glucose metabolism in the precuneus was measured using 18F-fluorodeoxyglucose (FDG) PET. Group comparisons were performed using the Wilcoxon rank-sum test. In a subsample with amyloid (11C-Pittsburgh compound B) and tau (18F-flortaucipir) PET, a mediation analysis tested whether the association between MBI and FDG uptake was mediated by AD pathology. The prevalence of MBI positivity was higher in carriers (68%) than non-carriers (35%) (p=0.041). Among the whole sample, MBI+ participants had lower FDG uptake (p=0.019) than MBI-. This difference was mainly driven by MBI+ carriers, which had lower FDG uptake than MBI- carriers (p=0.026). This association was partially (70%) mediated by AD pathology (p=0.011). Mutation carriers with MBI exhibited hypometabolism in an early AD-related region, partially explained by AD pathology, suggesting that MBI may serve as a risk factor for disease progression, with neuropsychiatric symptoms potentially preceding both neurodegeneration and cognitive impairment. MBI should be further investigated as a promising marker for identifying high-risk individuals who may benefit from prevention strategies.

POSTER NUMBER:
181

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Look There: A Study of Cerebellar Involvement in a Visually-Guided Saccade Task using MEG

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To perform a saccadic eye movement in response to a visual stimulus ("look there!"), a sensorimotor transformation is required. Previous invasive studies of saccadic eye movements in primates found that execution of accurate eye movements depends critically on the cerebellum, with the major output neurons of the cerebellum (the Purkinje cells) predicting the motion of the eye. We studied the cerebellar role in the execution of the saccadic eye movement in 8 adult human volunteers using magnetoencephalography (MEG). Here we show how the cerebellar vermis and the lateral cerebellum are differentially involved in the preparation and execution of saccadic eye movements. The earliest response was observed in the contralateral cerebellar lobules V-VI which are known to be involved in motor processing and attention. In agreement with the primate studies, we found that population activity in the cerebellar vermis (represented by the MEG source time courses) consistently preceded saccade onset by about 50 ms. The termination of the activity in the vermis was also significantly later the end of the eye movement. Both the vermis and the lateral cerebellum are involved during the execution of the eye movement. While the electrophysiology of the human brain has been studied extensively with both invasive and non-invasive methods, the cerebellum has been largely ignored. Our work contributes towards the development of methods to non-invasive imaging of cerebellar function in humans in vivo.

POSTER NUMBER:
182

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In vivo imaging of gadolinium-based contrast agent leakage in patients with cerebral amyloid angiopathy

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Cerebral amyloid angiopathy (CAA) is defined by deposition of amyloid-beta in the walls of leptomeningeal and small cortical vessels and is a leading cause of intracerebral hemorrhages. The precise mechanisms that precede bleeding are incompletely understood. Blood-brain barrier (BBB) leakage has been proposed to play a role in the early pathophysiology. This study aimed to measure gadolinium-based contrast agent leakage in vivo from the leptomeningeal and small cortical vessels in patients with CAA and non-CAA controls. 14 Patients with CAA and 7 non-CAA controls were included and underwent 3T brain MRI. A gadolinium-based contrast agent (Dotarem) was injected and pre- versus postcontrast T2-FLAIR and Dynamic Contrast Enhanced imaging were used to assess leakage of contrast agent from leptomeningeal and small parenchymal vessels respectively. Leakage from leptomeningeal vessels was observed in the form of sulcal CSF enhancements that were observed more often in patients (5(36%)) than controls (0(0%), p = 0.03), and related with markers of subtle bleeding (i.e. cortical superficial siderosis and microbleeds). Although not statistically significant, leakage from parenchymal vessels was numerically higher in patients (0.00035±0.00036) than controls (0.00005±0.00041, p = 0.12), an effect that appeared to be driven by leakage in the cortex rather than the white matter. In conclusion, this study shows that leakage of gadolinium-based contrast agent through the BBB can be measured in vivo in CAA from leptomeningeal vessels and likely also from cortical small vessels. Future studies need to determine if these measures of BBB leakage could serve as therapeutic biomarkers in CAA.

POSTER NUMBER:
183

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Vasomotion patterns in the visual cortex of mice undergoing high-frequency 40Hz visual stimulation

Investigators: K. A. Vom Eigen, S. J. Van Veluw, O. R. Bonnar

Background: The neurodegenerative diseases Alzheimer's disease (AD) and cerebral amyloid angiopathy (CAA) are characterized by an accumulation of amyloid-β in the brain. It has been proposed that promoting clearance of these protein aggregates may slow the progression of disease. Vasomotion, the spontaneous dilation of arterioles independent of blood flow, has been found to promote brain clearance along the glymphatic pathway and is reduced in both AD and CAA. Recent work has demonstrated that high-frequency 40Hz visual stimulation can entrain vasomotion, effectively enhancing perivascular clearance of amyloid-β. However, a fundamental knowledge gap remains in the real-time effects of 40Hz visual stimulation on vasomotion patterns. We address this question with in vivo 2-photon microscopy in mice.

Methods: We performed cranial window surgeries over the visual cortex of 3-month-old male C57BL/6 mice (n=8) and imaged arterioles using 2-photon microscopy while mice were head-fixed and unanesthetized. Mice underwent several 5-minute periods of visual stimulation (flashing checkerboard) at varying frequencies and durations (40Hz constant, 8Hz constant, 40Hz 5s on/15s off, 8Hz 5s on/15s off) and arterioles were imaged during and after stimulation. Arteriole diameters over time were extracted using ImageJ/Fiji (VasoMetrics), and fast Fourier transforms will be used to determine vessel oscillation frequencies (MATLAB).

Results/Discussion: Data analysis is currently ongoing. We aim to characterize differences in vasomotion patterns in response to high and low-frequency stimulation. Results from this experiment will add insight to the mechanism behind vasomotion entrainment in response to 40Hz stimulation and help interpret data from existing and future studies of brain clearance.

POSTER NUMBER:
184

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Sex Effects of Respiratory-Gated Auricular Vagal Afferent Nerve Stimulation (RAVANS) on the Regulation of the Central Autonomic Network in Major Depression

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Dysregulation of cardiac autonomic function has been implicated in the comorbidity of major depressive disorder (MDD) and cardiovascular disease. Given sex dependent alterations of brain circuitry involved in mood and cardiac autonomic regulation, sex-selective therapies targeting this circuitry may improve both mood and cardiovascular outcomes in MDD. This study evaluated the effects of a novel non-invasive neuromodulation approach - respiratory-gated auricular vagal afferent nerve stimulation (RAVANS) on the regulation of the central autonomic network and cardiac autonomic function in patients with recurrent MDD.

39 subjects with MDD (30 females, 9 males, age=59.7±1.7 years) were randomized to active RAVANS or sham stimulation during a 3T fMRI session while undergoing a mild visual stress reactivity task. Cardiac pulse was collected to assess the normalized High-Frequency component of heart rate variability (HFn-HRV), an index of parasympathetic (cardiovagal) regulation.

Active RAVANS administration was associated with significant activation of left hippocampus [T=5.52, p(FWE-corr)<0.001] and an increase in HFn-HRV (p=0.04) compared to sham. A significant increase in HFn-HRV was observed in female MDDs receiving active RAVANS compared to sham (p=0.02), while no significant differences were observed in male MDD subjects (p=0.8). Changes in HFn-HRV power in female, but not male MDD subjects receiving RAVANS, were significantly associated with left hippocampal activity (b=48.1, p=0.02).

Here we show significant sex-dependent effects of RAVANS on the central autonomic network and stress-response-associated cardiovagal response in MDD. These results provide initial evidence supporting potential beneficial effects of this novel intervention in the management of cardiac autonomic dysregulation in MDD patients.

POSTER NUMBER:
185

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Optimizing Study Startup Timelines in an Externally Funded Multiple Site Expanded Access Protocol for ALS participants at MGH

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Background: Amyotrophic lateral sclerosis (ALS) is a progressive neurodegenerative disorder. Expanded Access (EA) provides access to investigational treatments for patients ineligible for clinical trials. Given ALS's rapid progression, optimizing study startup timelines for participant enrollment is crucial.

Study startup timelines are impacted by contract negotiations, Institutional review board (IRB) approvals, site infrastructure, training, and regulatory requirements. Therefore, optimizing this process through expedited IRB approvals, streamlined site activation, and efficient screening of participants can improve efficiency and accelerate treatment access.

Hypothesis: Enhanced site infrastructure, including streamlined site activation, expedited IRB approvals, and efficient participant pre-screening and ALS clinical provider collaboration will optimize study startup timelines at MGH.

Methods: Study startup timelines, including overall study startup time, single IRB (sIRB) approval, MGH activation, and first participant enrollment, were analyzed for one EA multisite protocol and compared to literature-reported startup timelines for other multisite studies.

Results: The overall study startup time from protocol submission to IRB approval and first participant enrollment was 161 days. sIRB approval took 40 days. The time from site activation to first enrollment was 11 days, ranking in the top 10% of sites.

Conclusion: Enhanced site infrastructure, including streamlined site activation processes, expedited IRB approvals, ALS clinical provider collaboration, and efficient participant pre-screening was effective in optimizing study startup timelines compared to other multisite studies

POSTER NUMBER:
186

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Addressing Microglial Dysfunction in the CLN3-Related Lysosomal Disease

Investigators: S. Yasa, E. S. Butz, A. Colombo, E. Beckett, U. Chandrachud, L. Montore, S. Tschirner, M. Prestel, S. D. Sheridan, S. A. Muller, J. Groh, S. F. Lichtenthaler, S. Tahirovic, S. L. Cotman

Batten disease, a childhood-onset dementia and lysosomal storage disorder, arises from loss of function mutations in the CLN3 gene. This genetic defect disrupts lysosomal degradation, leading to progressive neurodegeneration. Recent research highlights the critical role of neuroinflammation and alterations in the immune system in driving disease progression. By understanding these neuroimmune mechanisms, we may identify novel therapeutic targets for managing the disorder.

Microglia, the primary immune cells in the nervous system, contain a higher number of lysosomes than most cell types. They are vital for degrading cellular debris and recycling materials, ensuring brain homeostasis. In our studies using Cln3Δex7/8 mice, a genetically accurate model of CLN3 disease, we investigated CLN3-deficient microglia and observed that the loss of CLN3 function in microglia leads to the accumulation of lysosomal storage materials and abnormal subcellular organelle morphology. Additionally, we identified pathological proteomic signatures that indicate impaired lysosomal function and disrupted lipid metabolism.

CLN3-deficient microglia displayed significant deficits in essential processes such as motility, phagocytosis, and myelin clearance, resulting in cholesterol accumulation and compromised myelin integrity in aged mice. These findings underscore the vital role of microglia in maintaining neuronal health and reveal how CLN3 loss diminishes their neuroprotective capabilities.

Encouragingly, treatments with autophagy inducers and cholesterol-lowering drugs effectively restored normal microglial function. This research suggests that targeting microglial dysfunction may offer a promising therapeutic avenue for managing CLN3-related diseases, highlighting the need for further exploration of immune-targeted therapies in this context.

Neurosciences

POSTER NUMBER:
187

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Detecting Covert Consciousness and Predicting Recovery after Severe Brain Injury: COMPASS Study Protocol

Investigators: J. Yeager, M. Fecchio, M. Cambareri, D. Shreier, M. Solvik, U. Górska-Klimowska, C. Brace, Y. Bodien, M. Young, M. Boly, B. Edlow

A patient's level of consciousness in the intensive care unit (ICU) significantly impacts their chances of long-term recovery and is a primary determinant of decisions about the withdrawal of life-sustaining therapy (WLST). However, there is often insufficient evidence to determine whether a behaviorally unresponsive patient is conscious and to determine their likelihood of recovering consciousness. As a result, families often make WLST decisions without clearly understanding their loved one's state of consciousness or potential for recovery.

Growing evidence supports the possibility that brain complexity—defined as the coexistence of local connectivity (specialization) and long-distance connectivity (integration)—is a reliable marker of consciousness. Transcranial magnetic stimulation electroencephalography (TMS-EEG) measures brain complexity using the perturbational complexity index (PCI), which has been validated to detect consciousness with a sensitivity of 95% in chronically brain-injured patients. This unparalleled sensitivity motivates our selection of TMS-EEG as the focus of this ICU research study.

The primary goals of our NIH-funded multi-center study are to demonstrate the diagnostic and prognostic utility of TMS-EEG measures of PCI by comparing it to 1) a composite reference standard for consciousness that combines behavior, task-based functional (fMRI), and task-based EEG in the ICU; and 2) scores on the Disability Rating Scale (DRS) at 6-months after hospital discharge, controlling for age and injury mechanism. Enrollment began in November 2024, and we aim to enroll 100 individuals with acute severe brain injury over five years.

POSTER NUMBER:
188

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Systematic comparison of resting-state vs. task-based brain parcellation for precision functional mapping

Investigators: D. Zhi, T. Ge

Precision mapping the brain into distinct functional regions is essential for understanding its organization, facilitating neuroscience research, and improving clinical interventions. However, current efforts to develop comprehensive brain parcellations are limited by the availability of large, homogeneous brain imaging datasets. While several atlases have been derived from resting-state fMRI data to reflect intrinsic brain organization, a robust and widely applicable task-based parcellation that captures a broad spectrum of functional domains remains missing. This limitation is particularly important because brain functional topography is dynamic and varies across different cognitive and behavioral states, emphasizing the need for a systematic approach to studying brain organization during both rest and task-related activity. Understanding these variations is critical for precise functional localization and advancing neuroscience research.

In this work, we introduce novel cortical parcellations derived from both resting-state and task-based fMRI using a hierarchical Bayesian parcellation framework. The task-based parcellation was generated from a diverse set of fMRI datasets, spanning a wide range of functional task domains. Our analysis reveals that this parcellation not only preserves the large-scale functional organization observed in existing resting-state atlases at the group level but also significantly improves the accuracy of functional localization at the individual level. By providing a more precise localizer for brain functional domains, our approach offers a practical tool for both cognitive neuroscience and clinical applications, paving the way for more personalized and functionally meaningful interpretations of brain imaging data.

POSTER NUMBER:
189

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Acetabular Labral Tear Size as a Predictor of Long-Term Outcomes and Conversion to Total Hip Arthroplasty: Minimum 8 Year Follow-Up

Investigators: S. S. Chenna, J. S. Mun, R. L. Poutre, B. J. Allen, S. M. Gillinov , B. S. Siddiq, N. J. Cherian, C. T. Eberlin, M. P. Kucharik , S. D. Martin

The labrum, cartilage in the hip socket, can tear. If left untreated, this injury can accelerate the progression of degenerative change within the hip joint, leading to early arthritis. Effects of labral tear size (LTS) on long-term patient-reported outcomes (PROMs) after hip arthroscopy (minimally invasive hip surgery) and the likelihood of hip replacement afterward are not understood well. This study included patients who underwent hip arthroscopy repairing symptomatic tears of the labrum by a single surgeon from 2002 to 2013; patients completed surveys assessing their postoperative function and pain. Patients ≤18 years of age, significant arthritis, and no labral tears were excluded. The patients included were sorted into two cohorts: small labral tear (SLT) and large labral tear (LLT). Of 154 patients (48.7% female; mean age±standard deviation(SD): 37.7±11.03), there was a mean±SD follow-up of 11.0±0.38 years and body mass index of 26.1±0.71 kg/m^2. Females had significantly more SLTs than males: 62.1% vs 37.9%. Those with SLTs experienced significantly better functional PROMs in daily activities and sports than those with LLTs. Even when accounting for other variables between patients, like demographics and findings during surgery, LTS can independently predict long-term PROMs. Patients with LLTs are 7.92 times significantly more likely than those with SLTs to undergo hip replacement afterward. These findings solidify labral tear size as a prognosticator of long-term PROMs after hip arthroscopy for symptomatic labral tears. As novel therapies to augment repairs become more prevalent, labral tear size can factor into identifying candidates who could most benefit.

POSTER NUMBER:
190

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Machine Learning Models Predict Pulmonary embolism in Patients Undergoing Total Hip Arthroplasty: An ACS-NSQIP Database Analysis

Investigators: M.H. Ilyas, P. Xiao, S. Afzal, A.E. Gemmy, L. Zhijun, M. Shimizu, Y.M. Kwon

INTRODUCTION: Pulmonary Embolism (PE) is a feared complication that is influenced by numerous host and surgical factors. Predicting PE after THA is difficult due to the wide range of patient characteristics and its low prevalence (under 0.5%), making traditional statistical methods inadequate. Machine learning (ML), however, has demonstrated promise in orthopaedic outcomes prediction by effectively analyzing the complex relationships between patient variables and surgical results. Therefore, this study aims to investigate the predictive power of ML models for PE following THA using a large, national patient database.

METHODS: We identified 269095 patients who underwent primary THA and were screened for PE as recorded on the (ACS-NSQIP) database from 2013 to 2023 using CPT code 27130. Four ML algorithms—ANN, RF, HGB, and KNN—were developed and trained to predict PE. Model performance was evaluated using receiver operating characteristic (ROC) curves, the area under the curve (AUC), calibration slopes, intercepts, and Brier scores.

RESULTS: In the final study cohort, 702 patients (0.26%) developed pulmonary embolism after primary THA. All ML models demonstrated great performance on the testing dataset when predicting PE with AUCs ranging from 0.82 to 0.92, calibration slopes between 0.37 and 1.03, and Brier scores between 0.004 and 0.005. KNN yielded the best prediction accuracy for PE, achieving an AUC of 0.92, a calibration slope of 1.02, a calibration intercept of 0.37, and a Brier score of 0.005. The strongest predictors for PE after THA were estimated probability of morbidity, preoperative serum sodium levels and total operation time.

Orthopedics/Sports Medicine

POSTER NUMBER:
191

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The influence of graft choice on quadriceps strength after ACL reconstruction

Investigators: G. Oliveira, M. Gonzalez, M. Mascarenhas, C. Leite, N. Mansur, G. Medina

Anterior cruciate ligament reconstruction (ACLR) is commonly performed, with approximately 100,000 to 200,000 cases annually in the United States. Strength deficits and muscle imbalances persist after ACLR, and isokinetic strength assessment is a key tool for evaluating quadriceps recovery. However, the impact of graft type on quadriceps strength remains unclear, particularly with the increasing use of quadriceps tendon autografts. The most recent systematic review on this topic was published in 2011, warranting an updated analysis incorporating recent studies. This systematic review and meta-analysis aimed to assess the effect of different graft types on quadriceps isokinetic strength at 6 and 12 months post-ACLR. The study followed PRISMA guidelines and was registered in PROSPERO (CRD42024564872). A comprehensive search in Embase, PubMed, and Cochrane databases identified studies comparing quadriceps isokinetic strength between at least two graft types. The primary outcome was Limb Symmetry Index (LSI) at testing speeds of 60°/s and 180°/s. A total of 46 studies were included in the systematic review, with six meeting criteria for meta-analysis. At 6 months, pooled analysis at 60°/s favored hamstring grafts (effect size: -12.77, $p < 0.01$), while no significant difference was observed at 180°/s. At 1 year, hamstring grafts maintained a significant advantage at both speeds ($p < 0.01$), with no observed heterogeneity across studies. Hamstring grafts demonstrate superior quadriceps strength recovery at 6 and 12 months post-ACLR. However, long-term recovery beyond 2 years remains unclear, highlighting the need for additional studies to determine whether quadriceps tendon grafts eventually achieve comparable strength outcomes.

POSTER NUMBER:
192

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Minimum 5-Year Outcomes of All-Arthroscopic Capsular Autograft Hip Labral Reconstruction

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Purpose: This study evaluated minimum 5-year functional and quality of life outcomes of hip acetabular labral repair with all-arthroscopic capsular autograft labral reconstruction.

Methods: Patients who underwent primary hip arthroscopy for arthroscopic capsular autograft labral reconstruction were included. Capsular autograft augmentation was performed if patients had a labrum with hypoplastic tissue (width<5mm), complex tearing, or frank degeneration of native tissue. Hip Outcome Score Activity of Daily Living/Sports Scale (HOS-ADL/SS), Modified Harris Hip Score (mHHS), and international Hip Outcome Tool-33 (iHOT-33) patient reported outcome measures (PROMs) were collected. Rates of minimal clinically important difference (MCID), patient acceptable symptom state (PASS), and substantial clinical benefit (SCB) were calculated for each PROMs at latest follow-up.

Results: Overall, 87 hips (86 patients) met inclusion criteria with a mean final follow-up of 64.0±7.2 months. Patients had a mean age of 39.5±10.7 years and body mass index of 25.7±4.1 kg/m2. The mean difference between baseline and latest follow-up for all 4 PROMs was statistically significant (P<0.001), with majority of patient improvement exceeding the MCID/PASS/SCB thresholds: iHOT-33:96.6/75.0/63.4%, HOS-ADL: 68.1/75.0/65.9%, HOS-SS:80.7/72.7/62.5%, mHHS:81.2/80/7/59.1%. 4 patients underwent conversion to total hip arthroplasty (4.6%) and no patients underwent revision hip arthroscopy (0.0%).

Conclusion: Here we show 87 hips that underwent labral repair with all-arthroscopic capsular autograft labral reconstruction that found excellent outcomes that exceeded the MCID/PASS/SCB thresholds in majority of patients at an average of 64.0±7.2 months follow-up. This novel technique offers the advantages of utilizing locally available tissue, preserving the chondrolabral junction, and minimizing significant donor-site morbidity.

POSTER NUMBER:
193

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The Relationship Between Foot Muscle Characteristics and Falls: An MRI-Based Evaluation

Investigators: A. Taseh, C. O'Neill, R. Joshi, J. Skolnik, J. Kwon, Z. Stewart, S. Ashkani-Esfahani, A. Tenforde

Background:Reduced foot muscle strength is a known risk factor for recurrent falls in older adults. Magnetic Resonance Imaging (MRI) studies indicate that foot muscle Cross-Sectional Area (CSA) correlates with strength, but its direct link to fall risk remains unclear. Understanding this relationship could improve fall prevention strategies. This study examines the association between foot muscle CSA and recurrent falls.

Materials and Methods: A retrospective case-control study included patients aged ≥60 years with recurrent falls (≥2) and matched controls without falls. Data on demographics, polypharmacy (≥5 medications), walking aid use, and lower extremity vascular disease or pain were collected. Foot muscle CSA at the first tarsometatarsal joint was measured on T1-weighted (n=8) or proton density (n=18) MRI using OsiriX Lite. Non-contractile tissues were excluded based on signal intensity. Two independent raters performed measurements, with interrater reliability assessed via Intraclass Correlation Coefficient (ICC). Multiple regression analysis adjusted for confounders. Statistical significance was set at $P < 0.05$.

Results: The study included 26 patients (13 cases, 13 controls; mean age 70.62 ± 8.54 vs. 69.46 ± 6.86 years; 38% female). CSA was significantly lower in cases (285.5 ± 220.17 mm^2) than controls (542.03 ± 218.62 mm^2; P=0.006). Interrater agreement was excellent (ICC=0.92, P<0.001). CSA remained inversely associated with recurrent falls [B = -280.28, 95% CI: (-499.6, -60.95), P = 0.03] after adjustment for other variables.

Conclusion: Lower foot muscle CSA is independently linked to recurrent falls, suggesting its potential role in fall risk assessment and intervention monitoring.

Orthopedics/Sports Medicine

POSTER NUMBER:
194

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Automated Readmission Prediction in Spine Oncology: A Natural Language Processing Approach to Clinical Documentation

Investigators: A. T. Zhang, A. Gholipour, D. Tobert

Background: Postoperative assessment in spine oncology, particularly for spinal metastases, is crucial due to the high morbidity and mortality associated with these procedures. Manual review of operative and discharge notes is time-consuming. Natural language processing (NLP) offers a solution by automating clinical insight extraction from unstructured text to predict readmission risks, improving outcomes and resource allocation.

Methods: We analyzed 363 patients who underwent spine metastases surgery at MGB institutions between 2016 and 2024. The cohort had a mean age of 66 years (range: 17-93), with 43.8% female patients (159/363). Operative and discharge notes were obtained from the Research Patient Data Registry (RPDR) and preprocessed by removing identifiers and combining relevant sections. Feature extraction employed Term Frequency–Inverse Document Frequency (TF-IDF) with unigrams and bigrams. Models including Logistic Regression, Random Forest, and Support Vector Machine (SVM) were trained and evaluated using stratified 5-fold cross-validation with accuracy, F1-score, and ROC-AUC.

Results: The unigram-SVM model performed best with TF-IDF features (Accuracy: 0.71; F1: 0.70), excelling in identifying negative cases (F1: 0.77). While common words like “continue” (0.0036) and “surgeries” (0.0028) were top predictive terms, clinically relevant terms such as “acute” (0.0015) and “tumor” (0.0015) among the top 30 words demonstrated meaningful feature extraction.

Conclusion: NLP enhances risk prediction in spinal metastases surgery. Future work focuses on expanding the clinical notes database and optimizing model performance through hyperparameter tuning and token validation to improve prediction accuracy.

POSTER NUMBER:
195

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Clinical Outcomes of MPFL Reconstruction in Pediatric Patients with First-Time Versus Recurrent Patella Dislocations: A Cohort Comparison

Investigators: S. F. Zotter, K. Reikersdorfer, G. Butler, W. S. Tung, C. Wright, N. Paschos

Patellofemoral instability is a common condition in pediatric patients, often leading to recurrent instability if not properly addressed. Medial patellofemoral ligament (MPFL) reconstruction is considered the gold standard for treating recurrent patella dislocations, offering stabilization and improved outcomes. Following a first-time patella dislocation surgery is indicated for patients with high recurrence risk or significant cartilage damage to prevent further instability. This study seeks to compare the clinical outcomes of MPFL reconstruction in pediatric patients following either first-time or recurrent patella dislocations. Data on demographics, risk factors for instability, and the mechanism of injury were collected. The primary outcome measured was failure, defined as a subsequent dislocation. Secondary outcomes included patient-reported outcome measures (IKDC, KOOS, and Lysholm scores), return to sport (RTS), and complication rates.

Forty-eight patients were included, with a median follow-up of 34.9 ± 11.9 months. No significant difference in failure rates was observed ($p = 0.73$). Both groups reported excellent patient outcomes, with no significant differences in IKDC, KOOS, and Lysholm scores (98 ± 3.3 vs. 96 ± 7.3, $p = 0.79$; 97 ± 4.5 vs. 94 ± 9.8, $p = 0.16$; 99 ± 2.0 vs. 99 ± 8.0, $p = 0.47$, respectively). The complication rate was also comparable between the recurrent and first-time dislocation groups (12.5% vs. 0%, $p = 0.15$). Our findings suggest that MPFL reconstruction following a recurrent patellofemoral dislocation shows similar failure rates, patient-reported outcomes, and complication rates compared to MPFL reconstruction in children and adolescents with first-time dislocations.

Population, Health Care Delivery, and Global Health Research

POSTER NUMBER:
196

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Strengthening Healthcare Training for Skin-Related Neglected Tropical Diseases: Addressing Gaps and Expanding Access

Investigators: S. Anwar, R. Geutjes, C. Fenenga, L. C. Fuller, J. Postigo, H. Utunen, R. Yotsu, E. E. Freeman

Introduction: Neglected tropical diseases (NTDs) are a group of infectious diseases that remain a major global health challenge. Most NTDs impact the skin and are collectively known as “skin NTDs”, including Buruli ulcer, chromoblastomycosis, cutaneous leishmaniasis, post-kala-azar dermal leishmaniasis, leprosy, lymphatic filariasis, mycetoma, onchocerciasis, podoconiosis, scabies, sporotrichosis, tungiasis, and yaws. Various initiatives have aimed to create training materials for frontline healthcare workers on diagnosing and treating these conditions. We evaluate existing skin NTD training materials to determine urgent needs for future resources.

Methods: We reviewed skin NTD training materials for frontline healthcare workers via the InfoNTD, OpenWHO, and Centers for Disease Control and Prevention websites for scope, year, geographic area of focus, language, format, and quality. Grey literature search was also completed to capture resources not included on these platforms.

Results: Out of 372 materials, 114 met inclusion criteria. The most common formats were text manuals (31%), online courses (29%), and web pages (26%). Most materials (71%) were available exclusively in English. Diagnosis, management, complications, and follow-up were covered in 78%, 90%, 57%, and 30% of resources respectively. Coverage of complications and follow-up were often limited, and no resources included follow-up of tungiasis. One third of materials did not include any images.

Conclusion: We emphasize vital gaps in current educational materials for healthcare workers on skin NTDs. There is a critical need for resources that offer detailed guidance on complications and follow-up care, incorporate high-quality images, and are translated into multiple languages to enhance capacity building and improve patient care.

Population, Health Care Delivery, and Global Health Research

POSTER NUMBER:
197

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Psychological Distress is Prevalent and Interdependent Among Patients with Decompensated Cirrhosis and Their Caregivers

Investigators: G. F. Bizup, M. E. Armstrong, A. N. Dalvi, N. Mason, K. Engel, K. A. O'Brien, S. Kenimer, M. S. Diop, A. El-Jawahri, N. N. Ufere

Patients with decompensated cirrhosis and their caregivers are at particular risk for psychological distress (i.e., anxiety and depression symptoms). However, little is known about the co-prevalence, or interdependence, of psychological distress among patient-caregiver dyads. In this cross-sectional study we examined the prevalence and co-prevalence of psychological distress (measured using the Hospital Anxiety and Depression Scale) among patients with decompensated cirrhosis and their caregivers. We used Actor-Partner Interdependence Modeling to examine whether psychological distress is interdependent within patient-caregiver dyads. This model tested whether each person's anxiety predicted their own depression (actor effects) as well as their partner's depression (partner effects).

Between 8/2018-9/2022 we enrolled 127 patient-caregiver dyads. Patients and caregivers reported similar rates of clinically significant anxiety (52% vs. 48%, p=0.59) and depression (41% vs. 35%, p=0.19) symptoms. Among dyads, 26% had both partners reporting clinically significant anxiety symptoms and 18% reporting clinically significant depression symptoms. Using Actor-Partner Interdependence Modeling, we found strong actor effects: greater anxiety was significantly associated with greater depression for both patients (β=0.50, $p<0.001$) and their caregivers (β=0.77, $p<0.001$). We identified one partner effect: here we show that greater caregiver anxiety was significantly associated with greater patient depression (β=0.20, p=0.02). Among patient-caregiver dyads, over 1 in 4 reported clinically significant anxiety symptoms and 1 in 6 reported clinically significant depression symptoms. Psychological distress was interdependent among dyads, with caregivers' anxiety significantly predicting patients' depression. These results underscore the need to develop behavioral health interventions to reduce psychological distress in both patients with decompensated cirrhosis and their caregivers.

Population, Health Care Delivery, and Global Health Research

POSTER NUMBER: **198**

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Value of an implementation trial on long-acting antiretroviral therapy for US persons with persistent HIV viremia

Investigators: R. Hu, P. P. Pei, J. Giardina, P. E. Sax, K. P. Reddy, E. P. Hyle, K. A. Freedberg

Background: Long-acting injectable antiretroviral therapy with cabotegravir/rilpivirine (CAB/RPV) may be effective for persons with HIV (PWH) who cannot adhere to daily oral therapy. We projected the monetary value of a clinical trial comparing standard clinic-based CAB/RPV support to CAB/RPV with intensive community support among PWH with persistent viremia in the US.

Methods: We simulated two strategies: 1) Clinic: standard clinic-based CAB/RPV delivery, and 2) InComm: CAB/RPV delivery in or outside traditional clinical settings with intensive community retention and adherence interventions. Using a microsimulation model, we estimated the value-of-a-trial (VOT) comparing Clinic with InComm. VOT considers both the value of reducing decision uncertainty and encouraging wider adoption of the optimal strategy post-trial. We simulated an estimated 10,000 US PWH with persistent viremia. Average 12-month-engagement-in-care for Clinic was 52% and for InComm 75%. Costs included CAB/RPV and standard clinic support ($2,990/month), and intensive support (additional $290/month) for InComm; these were varied across plausible uncertainty ranges.

Results: Clinic yielded 6.7 quality-adjusted life years (QALYs), and InComm 7.7 QALYs. At a willingness-to-pay threshold of $100,000/QALY, InComm was the optimal strategy in 68% of model iterations with an average incremental cost-effectiveness ratio of $83,000/life-year-saved. Estimated maximum Value-Of-the-Trial was $238 million. Results were most sensitive to cost and 12-month-engagement-in-care of the InComm strategy.

Conclusion: CAB/RPV with intensive community support would likely yield substantial clinical and survival benefits and be cost-effective for US PWH with persistent viremia. A trial of CAB/RPV with standard clinic versus intensive community support could provide value of up to $238 million.

POSTER NUMBER: **199**

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A preliminary cryopreservation protocol for Anopheles mosquito larvae

Investigators: Z. Chau, P. Joshi, A. Callahan-Muller, M. Toner, R. D. Sandlin

Mosquitoes serve as a vector for a variety of destructive diseases including malaria, West Nile, EEE, and Zika. Recent efforts to reduce the burden of these diseases have focused on genetic engineering to create mosquito strains that are sterile or incapable of carrying human disease. However, maintaining these new strains in the lab is expensive and there is a risk of genetic drift. Furthermore, genetic drift has made mosquito research less translatable to the wild since lab strains have deviated from wild mosquitoes. A potential solution to this problem is the cryopreservation of mosquitoes, allowing for indefinite storage of new and wild-type strains. Many other insect species have been preserved at the embryonic stage; however, mosquito embryos are not able to be made permeable to the cryoprotective agents (CPAs) necessary to prevent ice formation during cryopreservation. As a result, this work focuses on the development of a cryopreservation protocol for feeding-stage 1st instar Anopheles gambiae mosquito larvae. A working protocol would represent a significant step in the cryopreservation field, as a whole organism of this scale that is impermeable to CPAs has not been successfully preserved before. The cryopreservation protocol developed and tested in this study led to over 40% of cryopreserved larvae exhibiting partial reanimation within the first 24 hours following rewarming.

Population, Health Care Delivery, and Global Health Research

POSTER NUMBER:
200

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Prognostic Communication, Symptom Burden, Psychological Distress, and Quality of Life Among Patients with Decompensated Cirrhosis

Investigators: A. N. Dalvi, M. E. Armstrong, G. F. Bizup, N. M. Mason, K. G. Engel, K. A. O'Brien, S. M. Kenimer, M. S. Diop, A. R. El-Jawahri, N. N. Ufere

Timely prognostic communication is a critical component of care for patients with decompensated cirrhosis (DC). However, few studies have examined the association of prognostic communication with symptoms, mood, and health-related quality of life (HRQOL) in this population.

In this cross-sectional study of 218 outpatients with DC, we assessed their self-reported health status (terminally ill vs. not terminally ill), their prognostic communication with their hepatologists (Prognosis and Treatment Preferences Questionnaire), symptom burden (Revised Edmonton Symptom Assessment Scale), psychological distress (Hospital Anxiety and Depression Scale), and HRQOL (Short-Form Liver Disease Quality of Life scale). We used linear regression to examine associations among patients' self-reported health status and prognostic communication, symptom burden, psychological distress, and HRQOL.

Over 75% of patients reported that prognostic communication was helpful for making treatment decisions, maintaining hope, and coping with their disease. However, 81% had never discussed their end-of-life care wishes with their hepatologists. Overall, 36% self-reported a terminally ill health status which was associated with higher symptom burden (B=8.33, p=0.003), anxiety (B=1.97, p=0.001), and depression (B=2.01, p=0.001) and lower HRQOL (B=-7.22, p=0.002). Patients who wished they had more information on their prognosis reported higher symptom burden (B=7.14, p=0.010), anxiety (B=1.63, p=0.005), and depression (B=1.50, p=0.010) and lower HRQOL (B=-7.65, p=0.001).

While most patients with DC highly valued prognostic communication, the majority reported never discussing their end-of-life care preferences with their hepatologists. Self-reported terminally ill health status and inadequate prognostic communication were associated with poorer symptoms, mood, and HRQOL.

Population, Health Care Delivery, and Global Health Research

POSTER NUMBER:
201

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Cost-Effectiveness of Community Tuberculosis Screening in South Africa

Investigators: J. N. Deleger, S. N. Khatami, M. L. Jones, M. S. Jalali, A. D. Paltiel, E. B. Wong, K. A. Freedberg, R. Wood, C. R. Horsburgh, K. P. Reddy

Tuberculosis is a leading cause of death in South Africa. Early detection of asymptomatic tuberculosis could decrease tuberculosis transmission and deaths. The World Health Organization recommends systematic screening using digital chest radiography with computer-aided detection (dCXR) and/or rapid molecular diagnostics. The clinical and economic implications of these screening strategies remain unknown.

We used a microsimulation model to evaluate four community-based tuberculosis screening strategies for adults in South Africa: (1) 'No Screening'; (2) 'dCXR'; (3) sputum Xpert Ultra ('Xpert'); and (4) dCXR followed by sputum Xpert for those with an abnormal dCXR result ('dCXR+Xpert'). In the base case, sensitivity/specificity/cost for dCXR were 77%/65%/$18 for people living with HIV (PLWH) and 90%/73%/$18 for people living without HIV (PLWoH); for Xpert, they were 69%/98%/$29 for PLWH and 91%/99%/$29 for PLWoH. Incremental cost-effectiveness ratios (ICERs) ≤$3,000 per year-of-life saved (YLS) were considered cost-effective. We conducted sensitivity analysis around key parameters, including dCXR sensitivity/specificity/cost.

Base case results show that 'dCXR' identifies the most tuberculosis cases and produces the most false-positives, yielding higher life-years and costs as more people initiate tuberculosis treatment. 'dCXR+Xpert' produces the fewest false-positives, and 'Xpert' yields the fewest people initiating tuberculosis treatment. 'Xpert' and 'dCXR' produce ICERs below the cost-effectiveness threshold ($1,060/YLS and $1,330/YLS). In sensitivity analyses, 'dCXR+Xpert' becomes cost-effective only when dCXR sensitivity/specificity are higher and cost is lower.

In summary, community-based tuberculosis screening in South Africa with 'Xpert' or 'dCXR' would be cost-effective, if they could be scaled efficiently. Technological advances and cost reduction could make 'dCXR+Xpert' a cost-effective alternative.

Population, Health Care Delivery, and Global Health Research

POSTER NUMBER:
202

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Application of the Health Belief Model to Penicillin Allergy-Related Belief Patterns

Investigators: M. L. Eippert, D. C. Crabtree, R. Tam, O. Asupoto, L. R. Smith, K. G. Blumenthal, A. G. Wurcel

Most people who report a penicillin allergy are not truly allergic. Removing inaccurate penicillin allergy labels, known as de-labeling, is an evidence-based intervention that can improve clinical care. Despite cross-disciplinary support for penicillin allergy de-labeling, it is an uncommon practice outside visits with allergists. We analyzed 42 qualitative interviews of people who reported a penicillin allergy that had not previously been tested to create a content analysis of patients' beliefs of their allergy guided by the Health Belief Model. Belief domains include (1) level of belief of their allergy, (2) allergy history reaction risk, (3) amenability to penicillin allergy testing, and (4) anticipated acceptance of taking penicillin in the future provided testing disproved their allergy. We summarized these data in a Sankey diagram and identified the most common patient belief pathways. We found that while most people (n=28, 67%) had a strong belief that their allergy was true, the description of their allergy history was assessed as low risk (n=35, 83%). Additionally, most people were amenable to receiving a penicillin allergy test (n=39, 93%) and would either accept taking penicillin unconditionally (n=20, 48%) or situationally (n=12, 29%) if they received a negative test result. This study demonstrates the disconnect between a patient's belief in their allergy and the assessment of their true allergy risk. Since most patients were amenable to penicillin allergy testing, physicians may discuss allergy evaluations with their patients as a care improvement method. These findings will guide future implementation strategies to increase penicillin allergy de-labeling.

POSTER NUMBER:
203

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Estimating the Prevalence of Upper Extremity Motor Deficits in Acute and Chronic Stroke

Investigators: J. D. Hebert, J. DiCarlo, K. Takaoka, S. McKiernan, K. Emerson, K. A. Goode, D. J. Lin

Stroke affects over 800,000 new individuals annually in the United States, with approximately 7.8 million stroke survivors nationwide, and this population will only grow with a large aging generation. Upper extremity motor deficits are the largest source of stroke-related disability. However, previous studies have reported inconsistent prevalence of upper extremity deficits, ranging from 40-70% in acute stroke and 50-80% in chronic stages. Understanding prevalence rates is critical for informing clinical practice, rehabilitation strategies, and public health initiatives. We aimed to estimate the prevalence of upper extremity deficits in acute and chronic stroke patients utilizing information from medical records. Medical records from 1,917 patients seen at Massachusetts General Hospital for acute stroke from 2021 to 2023 were reviewed. Additionally, records from 251 Veterans with a confirmed chronic stroke diagnosis from 1999 to 2024 that were seen at the Providence Veterans Affairs Medical Center were screened. Presence of upper extremity deficit (defined as "weakness", "drift", or "ataxia") was recorded in both populations. In our data, over half of stroke survivors experience upper extremity deficit acutely after stroke (55.3%), and nearly a fourth of chronic stroke survivors are living with upper extremity deficit (24.3%). Chart review offers an accessible source for estimating general upper extremity motor function after acute stroke but provides broader insights of these deficits rather than precise measurements. Robust estimation of post-stroke upper extremity motor deficits is necessary to inform resource allocation, policy development, and targeted rehabilitation program designs including improvements in patient care.

Population, Health Care Delivery, and Global Health Research

POSTER NUMBER:
204

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Establishing the First Protocol and Clinical Indication Based Regional Diagnostic Reference Levels for Pediatric CT in the Middle East and North Africa: a Multicenter study of 38 Sites from 17 Countries

Investigators: L. Karout, A. Burade, J. Yametti, P. Kaviani, S. Hosseini, M. Kalra, MENA RadSafe Collaborators

Objective: We describe the framework and data characteristics for establishing body region- and clinical indication-based diagnostic reference levels (DRLs) and achievable doses (ADs) for pediatric CT in the Middle East and North Africa (MENA).

Materials and Methods: In collaboration with the Middle East Federation of Organizations of Medical Physics, we collected data from 34 imaging sites across 17 MENA countries, including 7,917 pediatric patients (<19 years; F:M, 3,168:4,749) who underwent head (n=2,979), chest (n=1,770), abdomen-pelvis (AP, n=1,943), or chest-abdomen-pelvis (CAP, n=1,225) CT. Data included patient demographics, clinical indications, CT scanner specifications, scan factors, and radiation doses [volume CT dose index (CTDIvol) and dose-length product (DLP)]. We estimated overall and site-specific 50th (AD) and 75th (DRL) percentile CTDIvol and DLP per body region and clinical indication. Non-normal data were compared using the Kruskal-Wallis test.

Results: Single-phase imaging was dominant (>85%) except for multiphase CAP-CT (~50%). Significant variations in CTDIvol and DLP were observed across sites, with MENA DRLs exceeding US levels by >50% for head, chest, and AP-CT exams in 62-68% of sites. Low-income countries had significantly higher doses than middle- and high-income countries ($p<0.001$).

Conclusion: Economic disparities and scanner distribution contribute to higher pediatric radiation doses in low-income MENA countries.

Clinical Implications: Addressing socioeconomic disparities through radiation dose education, protocol optimization, and CT technology upgrades is critical to improving pediatric imaging safety in the MENA region

Population, Health Care Delivery, and Global Health Research

POSTER NUMBER:
205

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Clinical and economic value of pre-travel health interventions for communicable diseases: A scoping review (1988-2023)

Investigators: S. Koiso, T. Stanic, N. F. Fields, N. M. Mulroy, E. T. Ryan, R. C. LaRocque, E. P. Hyle

Rationale for work: More people have been traveling internationally, increasing the risk for geographic spread of communicable diseases. Pretravel health interventions can reduce the communicable disease acquisition and the transmission risk during or after travel. To inform policy and research priorities, we present findings from a scoping literature review of studies that assessed the cost-effectiveness of pretravel interventions to reduce communicable diseases, including hepatitis A, traveler's diarrhea, and malaria, among others.

Key findings: From 1946-2023, only 44 published articles met the search criteria. Among them, 41% were published prior to 2000, and almost 40% exclusively focused on the prevention of hepatitis A. Interventions included passive immunization, vaccinations, and medications, with or without screening tests. Most studies found vaccination to be cost-effective compared with passive immunization and/or post-exposure treatment. Parameters with the greatest influence on an intervention's cost-effectiveness included: travel frequency and duration, endemicity at destination, type of traveler (i.e., business, leisure, visiting friends and relatives), testing and immunization costs, and behavioral factors (i.e., adherence to regimen, sexual behaviors, bed nets, prolonged stays in high-transmission areas).

Conclusions: The sparseness of analyses regarding pretravel interventions underscores the need for focused, cost-effectiveness evaluations of current travel-related practices. Further investigation of societal costs (i.e., productivity losses, loss of leisure time travel, informal caregiving resources), infection risks during travel, transmissions to others, and approaches to reduce intervention costs are needed. Such research may contribute to the development of clinical recommendations for specific groups of travelers and will be critical for informing health policies.

Population, Health Care Delivery, and Global Health Research

POSTER NUMBER:
206

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Predictors of Phlebotomy Failure in a Research Cohort Spanning the Normal Aging to Severe Dementia Continuum

Investigators: M. C. Pawlus, A. L. Gorharm , C. Suarez-Rodriguez, M. A. Galvez, A. Noori, A. Serrano-Pozo, Massachusetts Alzheimer's Disease Research Center

Blood-based (plasma and serum) research biomarkers hold promise for the diagnosis and prognostication of Alzheimer's disease in clinical practice. While venous blood collection in older adults with cognitive impairment can be empirically challenging, data on the predictors of phlebotomy success in this special population are scarce. We addressed this question in the 2015-2024 Massachusetts Alzheimer's Disease Research Center Longitudinal Cohort. Specifically, we hypothesized that age, sex, education, under-represented minority (URM) race/ethnicity, body mass index (BMI), and severity of cognitive impairment (i.e., Clinical Dementia Rating [CDR] global score) all impact the probability of phlebotomy success/failure.

To test this hypothesis, we first compared these characteristics across participants/visits with successful vs. failed phlebotomy via univariate analyses with t-test for continuous variables and Chi-squared test for categorical variables. Next, we built a mixed effects logistic regression model with phlebotomy success/failure as outcome variable; age, sex, education, URM, BMI, and CDR global score as fixed effects; and participant ID as random effect, to control for within-participant correlation of phlebotomy attempts across multiple visits.

Full data were available for 1,366 visits from 659 participants (mean [range]: 2.1 (1-7) visits per participant). Here we show that BMI (OR [95%CI]: 1.10 [1.05-1.16], p<0.001) and CDR global score (1.89 [1.22-2.94], p=0.005)—but not age, sex, or education—are independently associated with a higher probability of phlebotomy failure. URM were twice as likely to have a phlebotomy failure as Non-Hispanic Whites, but this trend did not reach statistical significance (2.04 [0.96-4.35], p=0.064). Potential mitigation strategies will be discussed.

POSTER NUMBER:
207

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Assessing the Feasibility of Implementing a Dementia Care Intervention to the Home-Based Primary Care Setting: A Pilot Study of Dementia Care Quality at Home

Investigators: A. J. Thacker, M. Sy, O. C. Sheehan, B. Leff, C. S. Ritchie

Approximately 7.5 million older adults are homebound, have difficulty and/or need assistance to leave their homes and approximately 50% of homebound older adults are living with dementia. Dementia care models were developed for traditional office-based primary care and have not been tailored to the unique needs of home-based primary care (HBPC) practices or the patients living with dementia (PLWD) they serve. We developed the Dementia Care Quality at Home (DCQH) intervention to enhance dementia care in HBPC and are evaluating its feasibility and acceptability in two HBPC practices. DCQH adapted existing dementia care models with input from HBPC clinicians, staff, and caregivers. The pilot study targeted 50 caregiver-patient dyads across two HBPC sites. Dementia champions implemented a baseline needs assessment and six modules covering medication review, safety, community resources, caregiver well-being, behavior management, and advance care planning. Feasibility outcomes showed that 86% (n=21) of practice staff found it easy to identify persons living with dementia, and 86% reported the assessments and modules were feasible. 54% of enrolled caregivers identified as racial or ethnic minorities. Among caregivers, 100% completed baseline assessments and at least one module, and 92.6% felt heard and supported. Satisfaction was high (90%), and Quality of Life in Alzheimer's Disease scores reflected positive experiences. The results of this pilot study show that DCQH is feasible to implement in HBPC and effectively serves diverse caregivers and patients. Findings support further testing in a larger trial to integrate DCQH into HBPC practices.

Psychiatry

POSTER NUMBER:
208

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A positive psychology-based intervention to increase physical activity after bariatric surgery

Investigators: N. A. Acharya, C. I. Castillo, S. H. Rachakonda, A. N. Thorndike, C. Psaros, N. A. Reilly-Harrington, J. C. Huffman, E. H. Feig

Despite metabolic and bariatric surgery (MBS) being the most effective treatment for severe obesity, 25% of these patients do not achieve long-term weight loss maintenance. Physical activity is important post-MBS, but most patients do not meet recommendations for moderate-to-vigorous physical activity (MVPA). Emotional barriers, such as fear of injury, lack of confidence, and weight stigma may contribute.

The Gaining Optimism After Weight Loss Surgery (GOALS) intervention tested feasibility, acceptability, and preliminary efficacy of a 10-week phone-based intervention to increase physical activity post-MBS by targeting positive affect during activity using positive psychology and motivational interviewing compared to a physical activity education/Fitbit control. Feasibility was measured as sessions completed and acceptability was measured using ease and utility ratings of each session topic (0-10 scale). Participants 6-12 months post-MBS at MGH with low physical activity were recruited. Assessments including actigraphy were conducted at baseline, post-intervention, and 24 weeks.

Forty-nine participants (M age = 44, 86% women) completed 9.6/10 sessions on average, showing high feasibility. Session ease and utility ratings ranged from 8.6 to 9.1/10, showing a high acceptability. MVPA increased by 9 min/week post intervention (effect size (ES) = 0.1) and 27 min/week at 24 weeks (ES = 0.3) for the intervention group compared to control. There was an improvement on attitudes related to exercise at both timepoints with medium-to-large ES.

In sum, GOALS was feasible, acceptable, and led small-to-large effect sizes improvements in MVPA and attitudes about physical activity. In the future, a larger scale efficacy trial should further test the intervention.

POSTER NUMBER:
209

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Depression and Suicidality in Early-Onset OCD

Investigators: H. Arcese, A. C. Jaroszewski, J. L. Greenberg, R. J. Jacoby, H. Weingarden, S. S. Hoepnner, S. Wilehlm

Obsessive-compulsive disorder (OCD) is a chronic condition that often co-occurs with major depressive disorder (MDD) and suicidal thoughts and behavior (STB). Early-onset OCD may increase the risk of MDD and STB through biopsychosocial pathways (e.g., chronic stress). Previous research on the relationship between early OCD onset, MDD onset, and STB remains unclear. Our study investigates these associations to inform early screening and intervention strategies.

We conducted a secondary analysis of a randomized controlled trial of a digital mental health intervention for OCD (N=120). Logistic regressions examined associations between age of OCD onset and (i) lifetime MDD, (ii) wishing to be dead (Q1 on Columbia-Suicide Severity Rating Scale [C-SSRS]), and (iii) active non-specific suicidal thoughts (Q2 on C-SSRS). Linear regressions explored relationships between (i) age of OCD onset and MDD onset, (ii) age of MDD onset with wishing to be dead and (iii) age of MDD onset with active non-specific suicidal thoughts.

The mean age of OCD onset was 14.7 years (SD=9.3), while the mean age of MDD onset was 18.2 years (SD=7.8). Earlier OCD onset was significantly associated with lifetime MDD (OR=0.94, $p<0.05$) and wishing to be dead (OR=0.95, $p<0.05$). Earlier OCD onset predicted earlier MDD onset ($\beta=0.42$, $p<0.01$), and earlier MDD onset was associated with wishing to be dead ($\beta=-0.02$, $p<0.01$) and active non-specific suicidal thoughts ($\beta=-0.01$, $p<0.05$).

Findings highlight the importance of depression and suicide risk screening in those with early-onset OCD and MDD. Early screening could potentially reduce the development of these comorbidities and mitigate long-term impairment.

POSTER NUMBER:
210

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Autistic Traits and Substance Use among Youth Experiencing Homelessness

Investigators: K. Burns, E. Neubauer, P. Ducharme, T. Wilens, C. Burke

Transitional age youth experiencing homelessness (TAY-EH, 16-25 years) are a large, marginalized group at high risk of substance use disorders (SUDs), psychiatric morbidity, and early mortality. There exists a dearth of evidence-based SUD and psychiatric treatments tailored to their unique needs and risk factors. Recent MGH research highlighted high rates of autistic traits in TAY receiving outpatient SUD care. It remains unclear if autistic traits represent an unexplored factor linking the experience of homelessness and SUD in TAY-EH. As part of an ongoing QA/QI assessment, the records of 49 TAY-EH from BOTW, a local psychosocial support agency serving TAY-EH, were reviewed. Patients completed the Social Responsiveness Scale (SRS) and the Screening to Brief Intervention (S2BI) during intake. After exclusion of 15 patients for concerns over data quality, 34 patients were included.

40% of youth scored in the moderate-severe range for autistic traits (e.g. T Score >65). TAY-EH at high risk for SUD had higher mean autistic trait scores (m(SD) of 66.3(10.5) for high SUD risk vs 57.6(6.1) for low SUD risk), and those at high SUD risk were significantly more likely to score in the moderate-severe range for autistic traits ($p=0.02$). In this group of TAY-EH, we found high rates of autistic traits, exceeding those seen in general/clinical youth populations. We also identified an association between higher autistic traits and SUD. These findings suggest that autistic traits may link the experience of homelessness and SUD in TAY-EH, offering a basis for developing targeted treatment interventions for this marginalized group.

POSTER NUMBER:
211

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Heart Rate and Heart Rate Variability Changes During Stimulation of rTMS targets

Investigators: T. A. Barbour, C. C. Carr, A. C. Wakhlu, J. C. Taylor, R. C. Garcia Gomez

Repetitive transcranial magnetic stimulation (rTMS) is an FDA-cleared treatment for treatment-resistant depression (TRD), typically targeting the left dorsolateral prefrontal cortex (DLPFC). However, response rates vary. To improve treatment response, individualized targeting methods such as resting-state functional connectivity (fMRI) and neuro-cardiac guided approaches based on heart rate (HR) changes have been explored. While promising, the relationship between autonomic changes, functional connectivity, and clinical response remains unclear.

17 patients enrolled in an accelerated rTMS treatment study underwent ECG recording while receiving intermittent theta burst stimulation (iTBS) at four cortical sites (F5, FC5, Beam F3, fMRI-determined) (100% resting motor threshold; 60 seconds). ECG traces were annotated to identify R-peaks using an automated algorithm followed by manual inspection. A point-process algorithm was then applied to quantify instantaneous measurements of HR and heart rate variability (HRV) within the spectral components of high-frequency (HF-HRV, 0.15 to 0.40 Hz) and low-frequency ranges (LF-HRV, 0.04 to 0.15 Hz). Normalized HF [HFn= (HF/(LF + HF))] was calculated as a measure of cardiovagal control dynamics. All measurements were estimated during TMS stimulation and baseline period.

A significant reduction in HR was observed across all stimulation sites compared to baseline ($p < 0.05$), with no significant differences between target locations. No significant changes in HFn were detected during stimulation.

These findings suggest that rTMS induces a general reduction in HR regardless of target site, without significant alterations in cardiovagal control. Further research is needed to elucidate the role of autonomic changes in rTMS response and their implications for personalized treatment strategies.

Psychiatry

POSTER NUMBER:
212

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Glutamatergic Medications for Obsessive-Compulsive and Related Disorders: A Systematic Review and Meta-Analysis

Investigators: D. R. Araujo Coelho, C. Yang, A. Suriaga, J. Manasa, P. A. Bain, W. F. Vieira, S. Papatheodorou, J. D. Salvi

Introduction: Obsessive-compulsive and related disorders (OCRDs) encompass various neuropsychiatric conditions that cause significant distress and impair daily functioning. Although standard treatments are often effective, approximately 60% of patients may not respond adequately, underscoring the need for novel therapeutic approaches. This systematic review and meta-analysis aimed to evaluate improvement in OCRD symptoms associated with glutamatergic medications. Methods: Electronic searches were conducted in PubMed, Embase, PsycINFO, Web of Science, and Cochrane Central Register of Controlled Trials on October 16, 2024, without date limits. Double-blind, placebo-controlled randomized clinical trials (RCTs) evaluating glutamatergic medications for OCRDs were included. Studies involving psychotherapy augmentation, non-English studies, abstracts, and protocols were excluded. Data were synthesized using random-effects meta-analyses. Outcomes included standardized mean difference (Cohen d) for OCRDs and reduction in Yale-Brown Obsessive-Compulsive Scale (Y-BOCS) scores for OCD. Results: A total of 27 RCTs (1369 participants; mean [SD] age, 31.5 [7.8] years; 65.6% female) were included. Glutamatergic medications showed a large effect size in improving OCRD symptoms (Cohen d = −0.80 [95% CI, −1.13 to −0.47]; low certainty of evidence). In the 23 OCD-specific RCTs, glutamatergic medications demonstrated a significant mean reduction in Y-BOCS scores (mean difference = −4.17 [95% CI, −5.82 to −2.52]; moderate certainty of evidence). Discussion: These findings suggest that glutamatergic medications may be beneficial for OCRDs, particularly OCD, with a large effect size observed. However, substantial heterogeneity among studies, variability in sample characteristics and treatment protocols, and potential publication bias limit the generalizability of the results.

POSTER NUMBER:
213

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Validation of electronic health record-based ascertainment of obsessive-compulsive disorder cases and controls

Investigators: B. Wang, A. Dankese, D. Yu, T. M. Fleming, J. Scharf, J. W. Smoller, L. Davis, PsycheMERGE Consortium

Obsessive-compulsive disorder (OCD) is a common psychiatric disorder, with two-thirds of affected individuals reporting severe impairment. Despite its significant burden, the etiology of OCD remains unknown, and existing treatments are often suboptimal. Recent genome-wide association studies (GWAS) have identified loci associated with OCD; however, the global genotyped sample size for OCD cases remains relatively small compared to other psychiatric disorders.

In this study, we leveraged electronic health records (EHR) linked to genomic data from two large hospital systems, namely Vanderbilt University Medical Center (VUMC) and Mass General Brigham (MGB), to develop and validate a high-throughput OCD phenotyping algorithm that integrates natural language processing (NLP), diagnostic codes, and medication records to identify relevant evidence across sites.

Expert chart reviews found that the algorithm combining both ICD codes and NLP on clinical notes achieved higher positive predictive values (PPV) for OCD cases at both sites (0.84 at VUMC and 0.91 at MGB) compared to using either ICD codes or NLP alone, albeit with a lower yield in OCD case identification. Significant associations were observed between identified OCD cases and OCD polygenic risk scores calculated using the latest OCD GWAS, at both sites. In conclusion, our study presents a scalable and cost-efficient approach to improving case ascertainment for OCD genomic studies, thereby contributing to a better understanding of OCD and its etiology.

POSTER NUMBER:
214

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Objective vs. Subjective Measures of Sleep Quality in Autism Spectrum Disorder

Investigators: V. A. Dixon, P. Hickey Townsend, N. B. Massa, K. Ostrow, A. Tolosa, D. Mylonas, L. Jones, A. Neumeyer, D. S. Manoach, Sleep, Cognition and Neuropsychiatry Lab

Sleep disturbances are common in autism and contribute to daytime dysfunction. EEG-derived measures objectively index sleep quality but may not reflect subjective experiences. We investigated whether subjective reports of sleep quality are accurate and if this differs in autism. 109 adolescents (71 autistic, 47 male; 38 typically developing, TD, 16 male) ages 12-19 (15.0±2.3) wore the Dreem3 EEG headband for 3 nights which provided wake after sleep onset (WASO) and sleep fragmentation index (SFI) measures. The PROMIS Sleep Disturbance (PSD), PROMIS Sleep Related Impairment (PSRI), and Pittsburg Sleep Quality Index (PSQI) questionnaires indexed subjective sleep quality. Using linear regression, we tested if objective measures predicted subjective ratings, and if the relationships varied by group. Objective ($ts \geq 2.96$, $ps \leq .01$) and subjective sleep quality was worse in autistic participants ($ts \geq 2.50$, $ps \leq .01$). Neither SFI ($Fs \leq 3.71$, $ps \geq .06$) nor WASO predicted subjective sleep quality ($Fs \leq .11$, $ps \geq .75$). There were no Group*SFI nor Group*WASO interactions ($Fs \leq .87$, $ps \geq .35$). Here we find discrepancies between objective and subjective sleep quality measures in both autistic and TD participants. Subjective reports may not be accurate in capturing sleep disturbances. Additionally, subjective questionnaires evaluate sleep quality over a longer timescale (weeks) and consider additional factors, such as sleep onset latency and impact on daily functioning, while objective measures may better capture variability in sleep across nights and certain aspects of sleep quality. Subjective measures should not substitute objective measures in sleep studies.

POSTER NUMBER:
215

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Temporal trends in Smoking, Vaping, and Cessation Attempts, Among Adults with Psychotic Disorders In The US

Investigators: O. A. Erinoso, J. Streck, O. A. Evins, Center for Addiction Medicine

INTRODUCTION: The aim of this study was to examine temporal trends in cigarette smoking and vaping, as well as cessation attempts between adults with and without Psychotic Disorders (PDs). We hypothesized a decreasing trend in smoking and vaping in both groups, and individuals without PDs would have higher odds of past-year cessation attempts.

METHODS: Data were drawn from Waves 4–7 (2016–2023) of the Population Assessment of Tobacco and Health (PATH) Study, comprising 46,974 adults (≥18 years), including 1.4% with a self-reported past-year PD diagnosis. Outcomes were current cigarette smoking, vaping, any past-year cigarette and e-cigarette cessation attempt. Poisson regression with a log link and interaction between survey wave and PD-status estimated adjusted prevalence ratios (APR), while generalized estimating equations examined the odds of any cessation attempt. Models were weighted and adjusted for demographics and past-month drug or alcohol use.

RESULTS: Over time (2016-2023), smoking declined (PD-APR: 24.7%-22.8%; non-PD-APR: 18.0%-13.5%) while vaping increased (PD-APRs: 8.0%-11.3%; non-PD-APR: 3.4%-6.8%), but adults with PD had consistently higher smoking and vaping prevalence. Interaction between PD status and time showed significant modifying effects ($p < 0.05$), specifically in 2018/19 and 2021. Among individuals who smoke, adults with PD had 66% higher odds of a cessation attempt (95% CI: 1.2-2.2), and among vapers, the odds were 2.7 times higher (95% CI:1.7-4.1).

CONCLUSION: Despite the higher prevalence of smoking and vaping among adults with PD, cessation attempts are higher. These results underscore the need for targeted support to translate these quit attempts into successful smoking and vaping cessation.

Psychiatry

POSTER NUMBER:
216

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Promoting exercise in type 2 diabetes: A novel psychological-behavioral intervention and randomized controlled trial design

Investigators: J. Fan, C. Celano, C. Massey, C. Bedoya, D. Wexler, J. Huffman

Background: The American Diabetes Association recommends individuals with type 2 diabetes (T2D) perform at least 150 minutes of moderate to vigorous physical activity (MVPA) weekly. However, many struggle to meet these guidelines. Motivational interviewing (MI), a validated approach to behavior change, has shown modest success in increasing physical activity, but may not sufficiently improve health outcomes. Positive psychology (PP), significantly linked with physical activity and health outcomes, may boost these behaviors. This randomized controlled trial aims to evaluate the efficacy of a 16-week, phone-based, combined PP-MI intervention to improve physical activity and enhance well-being in 280 adults with T2D.

Methods: Adults with T2D and low MVPA (<150 minutes/week) will be randomized to receive either the PP-MI or MI-alone intervention. Over 16 weeks, individuals will complete nine weekly phone sessions with a study interventionist and receive twice-weekly text messages. Individuals in the PP-MI condition will engage in weekly PP activities (e.g. gratitude for positive events) and set physical activity goals. Those in the MI-alone condition will complete health behavior adherence tasks. The primary outcome will be accelerometer-measured physical activity, assessed at baseline and 8-, 16-, 24-, and 52-weeks post-randomization. Secondary outcomes include psychological, functional, and health behavior measures.

Results: Recruitment began in October 2022. We hypothesize that the PP-MI intervention will result in significantly higher MVPA and greater improvements in health outcomes compared to MI-alone.

Discussion: This trial will provide critical information regarding the efficacy of a PP-MI intervention, which may benefit adults with T2D and impact public health at large.

POSTER NUMBER:
217

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Accelerated Intermittent Theta-Burst Stimulation (iTBS) to the Right IPL Reduces Suicidality in a Single Day of Treatment

Investigators: H. Ghosh, S. Chowdhury, K. T. Donaldson, M. O'Connor, O. Newman, S. Walsh, T. Barbour, K. Ellard, L. Neng, J. Camprodon

Background: Electroconvulsive therapy (ECT) reduces suicidal ideation by altering the brain's functional connectivity. Our group's previous work has demonstrated that after ECT, increased functional connectivity between the anterior cingulate cortex (ACC) and the right inferior parietal lobule (IPL) correlates with reduced suicidal ideation. We hypothesize that focally targeting the IPL with transcranial magnetic stimulation (TMS) will increase ACC-IPL connectivity and reduce suicidal ideation. Here, we present results from an open-label accelerated TMS study and an ongoing mechanistic randomized controlled trial (RCT).

Methods: We recruited 10 patients exhibiting moderate-to-high suicidality. Patients received accelerated intermittent theta-burst stimulation (iTBS) to the right-IPL cluster of the Executive Control Network (ECN). We identified patient-specific right-IPL coordinates using fMRI-connectomics. Patients received 10 iTBS sessions in one day (18000 pulses;120% of MT). We collected clinical and resting-state fMRI data before and after administering iTBS. The RCT utilizes the same neuromodulation protocol, but randomly assigns patients to active or sham TMS.

Results: After 1 day of accelerated iTBS to the right-IPL, we observed a 48% reduction on the ideation subscale of the Columbia-Suicide Severity Rating Scale (t=2.71; p=0.024) and an increase in ACC-IPL functional connectivity (Cohen's d=0.78), which supports our response biomarker hypotheses. Analyses for the ongoing RCT will be presented.

Conclusions: Rapid and effective antisuicidal therapies are urgently needed. We present results from a novel precision treatment strategy. This accelerated precision neuromodulation protocol effectively engages the target biomarker (increase in ACC-IPL functional connectivity) and shows clinical efficacy (48% reduction in suicidal ideation) after 1 day of treatment.

POSTER NUMBER:
218

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Comparison of augmentation with aripiprazole or repetitive transcranial magnetic stimulation versus switching to the antidepressant venlafaxine on quality of life and cognition in subjects with treatment resistant depression

Investigators: C. Guidetti, G. Papakostas, M. Trivedi, R. Shelton, D. Iosifescu, M. Thase, M. Jha, S. Mathew, C. De Battista, M. Dokucu, O. Brawman-Mintzer, S. Chaikali, L. MacGregor, T. Carmody, M. Fava

Objective: This study compared the effects of augmenting antidepressants with aripiprazole or repetitive transcranial magnetic stimulation (rTMS) versus switching to venlafaxine XR/duloxetine on quality of life (QoL) among patients with TRD.

Methods: In a pre-defined secondary analysis of a multi-site, open-label, effectiveness trial, patients with TRD were randomly assigned to aripiprazole augmentation, rTMS augmentation, or switching to venlafaxine XR/duloxetine in a 1:1:1 ratio and they were treated for 8 weeks. TRD was defined as an inadequate response to two or more antidepressant trials of adequate dose and duration, as defined by the MGH ATRQ. QoL was pre-defined as a key secondary endpoint for this study and assessed using the short form of the quality-of-life enjoyment satisfaction scale (Q-LES-Q-SF). A mixed-effects model with repeated measures (MMRM) was applied. This study was conducted from 07/13/2017 to 12/22/2021.

Results: Among 258 randomized participants with at least one post-baseline Q-LES-Q-SF measurement, augmentation with aripiprazole demonstrated statistically significant superiority over switching on the Q-LES-Q-SF (p=0.002), while rTMS did not (p=0.326). At endpoint, changes from baseline in the Q-LES-Q-SF scores were 10.61 (SE=1.0) for aripiprazole augmentation, 11.59 (SE=1.1) for rTMS augmentation, and 8.68 (SE=0.9) for venlafaxine XR/duloxetine switch.

Conclusion: Augmentation with aripiprazole, but not rTMS, improved QoL significantly versus venlafaxine XR/duloxetine switch in TRD patients. However, a much smaller than expected sample size for the rTMS group may explain the lack of statistical significance.

Psychiatry

POSTER NUMBER:
219

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Varenicline for Youth Nicotine Vaping Cessation: A Randomized Controlled Trial

Investigators: A. E. Evins, C. Cather, H. T. Reeder, B. Evohr, B. O. Kelly, N. F. Hasan, K. Potter, G. N. Pachas, K. M. Gray, S. Levy, N. A. Rigotti, V. Iroegbulem, J. Dufour, K. Casottana, M. A. Costello, J. M. Gilman, R. M. Schuster, Center for Addiction Medicine

Electronic cigarette use (vaping) among adolescents and young adults is common, yet few treatments have been tested in this population. This study aimed to evaluate the efficacy of varenicline for nicotine vaping cessation in youth who do not smoke tobacco regularly. We conducted a three-group randomized clinical trial comparing 12 weeks of double-blind varenicline versus placebo, each combined with brief, remotely-delivered behavioral counseling, and compared to enhanced usual care, with monthly follow-up to 24 weeks. The trial took place at a single U.S. site from June 2022 to May 2024. Participants included youth aged 16-25 who vaped nicotine daily or near daily and wanted to reduce or quit vaping. Participants were randomized to 12 weeks of varenicline with weekly counseling (n=88), placebo with weekly counseling (n=87), or enhanced usual care (n=86). All participants received a referral to text messaging vaping cessation support. The primary outcome was biochemically verified continuous vaping abstinence for the last 4 weeks of varenicline treatment versus placebo. Secondary outcomes included bio-verified continuous abstinence from weeks 9-24 in the varenicline and placebo groups, and comparisons with enhanced usual care. A total of 261 participants were randomized (mean age 21.4 years, 53.3% female), and 258 completed the trial (98.9%). Varenicline showed superior continuous abstinence rates compared to placebo and enhanced usual care. Varenicline, combined with behavioral counseling, increased vaping abstinence in youth who vape nicotine and do not regularly smoke tobacco.

Psychiatry

POSTER NUMBER:
220

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Reach for Health Study: A novel behavioral intervention and randomized controlled trial design to promote adherence in heart failure.

Investigators: I. Henneman, C. Celano, C. Massey, E. Feig, W. Chung, J. Huffman

Heart failure (HF) affects over 6 million Americans and is associated with poor health outcomes including reduced health-related quality of life, frequent hospitalizations, and high rates of mortality. Adherence to cardiovascular health behaviors, such as physical activity (PA), a low-sodium diet, and medications, can improve outcomes. Positive psychology (PP) and motivational interviewing (MI) have been successful in increasing adherence and well-being in related populations. Accordingly, the REACH study will test a 12-week, phone-delivered PP-MI intervention with weekly health behavior focused text messages in a randomized trial of 280 patients with HF.

Eligible adults will be randomized to the PP-MI intervention or an MI-alone educational control condition. Both groups will complete 12 weekly phone sessions and receive twice weekly health behavior text messages for 24 weeks. PP-MI participants will engage in weekly PP activities and will work towards PA, diet, and/or medication goals each week. Those in the MI-alone condition will receive MI-informed education related to these health behaviors. The study's primary outcome (composite of PA [accelerometer], sodium intake [urine sodium], and medication adherence [electronic pill bottle]), will be assessed at baseline, Weeks 12, 24, and 48. Psychological, functional, and cardiac health outcomes will also be assessed.

Recruitment for the study began in December 2021. We hypothesize that the PP-MI intervention will significantly improve health behavior adherence, psychological, functional and HF symptom outcomes, with potential but non-significant cardiac health improvements.

To conclude, this trial will provide critical information regarding the PP-MI intervention's efficacy, which could benefit HF patients and public health.

POSTER NUMBER:
221

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Does the Treatment of High-Risk Youth with Mood Disorders Reduce Later Substance Use Disorders: A Mid-point Analysis

Investigators: A. Kim, K. Burns, A. Yule, M. DiSalvo, T. E. Wilens

Mood disorders, including major depressive disorder (MDD), place individuals at a higher risk for the development of substance use disorders (SUD). Individuals with comorbid MDD and SUD have worse outcomes than individuals with either of these disorders alone, highlighting the importance of investigating the link between these psychopathologies. As part of an NIH longitudinal study, we examined if treatment of MDD mitigates the trajectory or later development of SUD in youths at higher risk for substance use.

This preliminary analysis included a sample of youths ages 16 to 30 years recruited from behavioral health centers at large academic medical centers in Boston. 88 individuals were identified to have subthreshold or full depression diagnoses based on SAGE-SR, an online structured clinical interview.

Using logistic regression models controlling for propensity scores, we found clinically significant, albeit not statistically significant findings. Those who received MDD treatment had 33% reduced odds (OR=0.67, 95% CI: 0.03-15.82, p=0.80) for developing an SUD compared to those with no MDD treatment. Despite the lack of statistical significance at midpoint, these observational analyses highlight the potential protective effect of treatment on the trajectory of SUD in high-risk youths.

POSTER NUMBER:
222

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Medical Provider Perspectives on Chronic Pain Treatment for Underserved Spanish-speaking Latine Patients at Community Health Clinics

Investigators: Y. Kim, N. Giraldo Santiago, N. Alvarez Frank, J. Greenberg, M. Cardoza

Background: Spanish-speaking Latine individuals with chronic pain are underserved in medical settings in the US, in part due to linguistic and cultural limitations in existing interventions. We seek to tailor a mind-body intervention to better meet this population's needs by identifying prominent challenges and potential adaptations based on insights from their medical providers.

Methods: We conducted qualitative focus groups with medical providers (N = 4 groups; 15 providers) who work with Spanish-speaking Latine patients experiencing chronic pain at MGH Healthcare Centers. Using rapid qualitative data analysis, we identified key barriers to engagement in mind-body treatments for chronic and potential culturally responsive adaptations.

Results: Providers identified two primary barriers: (1) skepticism towards mind-body interventions and mental health stigma and (2) systemic obstacles to care (e.g., lack of culturally and linguistically tailored services, the shift from community-based to urgent care models, stress from multiple jobs to meet financial needs, geographical segregation from healthcare centers). To address these challenges, providers suggested (1) integrating family and community (e.g., interventions led by community health workers or community members and incorporating family for accountability and logistical support) and (2) integrating intentional spaces for connection to foster social support and engagement.

Conclusion: Our findings highlight intersecting barriers to care for Latine Spanish-speaking patients with chronic pain, underscoring the need for culturally and linguistically adapted interventions and showing that a community- and family-aligned approach can enhance accessibility and engagement. Currently, we are conducting focus groups to incorporate patient perspectives, ensuring that their voices shape the program adaptation.

Psychiatry

POSTER NUMBER:
223

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Abnormal Thalamocortical Circuit Functioning During Wake and Sleep in Phelan McDermid Syndrome

Investigators: N. B. Massa, P. Hickey Townsend, V. A. Dixon, K. Ostrow, D. Mylonas, L. Jones, A. Neumeyer, D. S. Manoach

Thalamocortical circuitry (TCC) may be altered in autism and underlie sleep disturbances and sensory sensitivities. TCC filters sensory information, preventing arousals during sleep and sensory overload during wake. Here, we evaluate if TCC is altered in Phelan McDermid Syndrome (PMS), a genetic syndrome with an autism-like phenotype characterized by sleep disturbances and intellectual disability. PMS stems from mutations in SHANK3, a gene regulating communication between inhibitory-excitatory synapses within TCC. We predict that individuals with PMS will have altered TCC, indexed by reduced sleep spindles and 40Hz auditory steady-state responses (ASSRs), EEG signatures arising from TCC. We predict TCC dysfunction will also lead to poorer sleep quality. Adolescents ages 12-19 (PMS, n=6; Typically Developing (TD), n=39) slept three nights wearing an EEG headband. During wake, EEG was recorded while participants (PMS, n=2; TD, n=12) listened to 40Hz noise bursts to measure ASSRs. We derived sleep spindle density (#/min) from sleep data and calculated inter-trial phase coherence (ITPC) from ASSR data. PMS participants had poorer sleep quality compared to TD (Wake After Sleep Onset, $t(43)=2.54$, $p=.015$; Sleep Fragmentation Index, $t(43)=2.67$, $p=.01$). Spindle density was reduced in PMS during N2 sleep compared to TD ($t(43)=-3.13$, $p=.008$). Additionally, both PMS participants had ASSRs 1.75 standard deviations below TD. These preliminary results support that SHANK3 mutations disrupt TCC and that TCC dysfunction may contribute to sleep disturbances more broadly in idiopathic autism.

POSTER NUMBER:
224

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All in My Head? Brain Structure Morphology and Socioenvironmental Factors in the Symptomatology of Adult Post-Traumatic Stress Disorder

Investigators: C. W. McFarland, H. Garrison-Desany, C. A. Denckla, The AURORA Cohort

Post-traumatic stress disorder (PTSD) is a psychiatric disorder that is increasingly linked with brain structure morphology; however, there exists conflicting evidence regarding which structural differences are involved. In addition, emerging literature indicates interactions between socioenvironmental factors and neuroanatomy, yet the interplay between structural differences and socioenvironmental factors in adult PTSD symptomatology remains unexplored.

To address this, I conducted secondary analyses on 343 participants from the AURORA cohort, a longitudinal multi-site assessment of post-traumatic neuropsychiatric sequelae. Zero-inflated negative binomial analyses were employed to evaluate the relationship between the morphology of 16 select brain regions collected via MRI and PTSD symptoms assessed via the DSM-5 at and between two weeks and six months post-trauma, adjusting for socioenvironmental factors. Finally, I investigated interactions of sex, race/ethnicity, and socioeconomic status (SES), and performed a detailed missingness analysis given the potential for PTSD to affect ongoing participation.

Here, I present novel findings that larger left and right thalamic volumes two weeks post-trauma predicted an absence of PTSD symptoms six months later. Larger thalamic and left hippocampal volume correlated with an absence of PTSD symptom severity two weeks post-trauma. For the first time, lateral ventricular volume was identified as a negative structural correlate of PTSD symptom severity. Lastly, novel sex-specific and SES-based associations between amygdala, thalamic, and hippocampal volumes and PTSD symptom severity were identified.

These findings underscore considering social and biological dimensions in the understanding, diagnosis, and treatment of PTSD, and suggest that neuroanatomies warrant further investigation as potential mechanisms in the pathogenesis of PTSD.

Psychiatry

POSTER NUMBER:
225

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A novel psychological-behavioral intervention to promote physical activity in patients with acute coronary syndrome

Investigators: E. J. McGranaghan, C. M. Celano, K. T. Rosenblum, N. B. Acharya, C. N. Massey, J. C. Huffman

Background: Physical activity following Acute Coronary Syndrome (ACS) is important for reducing health risks; however, most patients struggle to remain active. Positive Psychology (PP) and Motivational Interviewing (MI) interventions demonstrate potential for enhancing well-being and reducing motivational barriers to increasing activity. A novel intervention for ACS that combines both PP and MI may be effective for ACS recovery and increasing physical activity. This randomized controlled trial examines the efficacy of a 24-week, remotely delivered PP-MI intervention for 280 post-ACS patients.

Methods: The intervention includes 12 weeks of phone sessions with a study trainer and 24 weeks of twice-weekly text messages. During sessions, participants review prior goals, are assigned new PP exercises, and set a physical activity goal for the following week. The PP component focuses on gratitude, strengths, and meaning, each grouped into four-week modules to support incorporation into daily life. The MI component focuses on setting specific and attainable physical activity goals, utilizing resources to increase activity, and identifying and overcoming barriers to physical activity.

The PP-MI condition will be compared to standard post-ACS treatment. The primary study outcome is accelerometer-measured moderate-to-vigorous physical activity (MVPA) post-intervention, with secondary outcomes examining psychological, functional, biological, and cardiac-event-related factors. Primary and secondary outcomes are assessed at 12, 24, and 48 weeks.

Results: Recruitment is ongoing and is anticipated to be completed upon enrolling 280 participants.

Conclusions: If effective, this program has the potential to benefit ACS patients and address the widespread public health issue of low physical activity.

Psychiatry

POSTER NUMBER:
226

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An Open-Label Trial Examining the Safety and Efficacy of Transcranial Photobiomodulation for the Treatment of Autistic Traits in Children and Adolescents with ADHD

Investigators: M. O'Connor, T. A. Ceranoglu, M. DiSalvo, C. Hutt Vater, G. Joshi

Introduction: Transcranial Photobiomodulation (tPBM) is a therapeutic treatment that uses non-ionizing electromagnetic wave to stimulate brain activity. This study sought to assess the efficacy and safety of tPBM in children and adolescents with attention deficit/ hyperactivity (ADHD) and autistic traits(ATs).

Methods: Participants with ADHD and comorbid ATs aged 9-17 received daily tPBM treatments in an open-label single group design. Autism spectrum disorder (ASD) symptom severity was measured using the Clinical Global Impression of improvement (CGI-I) scale and Social Responsiveness Scale-2nd Edition (SRS-2). Responder criteria was defined as reduction of ATs between baseline and endpoint, measured by ≥25% reduction in the SRS-2 and endpoint score of ≤2 on the CGI-ASD-I. Results were analyzed using a longitudinal mixed-effects regression model.

Results: 31 participants (mean age: 12.5 ± 3.0) were enrolled and included in the analysis. At endpoint, 13 participants (42%) had ≥25% reduction in SRS-2 score and 17 participants (55%) had a CGI-ASD-I score < 2. Our analysis yielded significant results ($p < 0.001$) in the SRS-2, MGH Social-Emotional Competence Scale (clinician- and parent-rated), Global Assessment of Functioning Scale, and ADHD Symptom Checklist. 27 participants (87%) reported an adverse event during the study, the most common were warmth at application site (10%) and headache (6%). No severe or serious adverse events were reported.

Conclusions: Daily tPBM treatment was well tolerated and was associated with improvement in autistic traits and executive function deficits in patients with ADHD. Further research into its efficacy in treatment of core features of ASD is warranted.

POSTER NUMBER:
227

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Elevated Psychological Pain and Related Symptoms among Sexual Minority Young Adults

Investigators: A. Preda, D. Robinaugh, A. Baker, T. Rodebaugh, M. Frumkin

Background. Sexual minority young adults experience worse mental health outcomes than heterosexual peers, including increased risk of depression and suicide. Psychological pain, a painful affective experience, may play an important role in these outcomes. The present study examines the severity of psychological pain in a large, diverse sample of sexual minority and heterosexual young adults.

Method. A cross-sectional sample of undergraduate students (N = 1481) at a small liberal arts college self-reported sexual orientation, psychological pain, depression, and loneliness. We ran simple and multiple linear regressions to examine the relative contribution of sexual minority status, depression, and loneliness to psychological pain scores.

Results. Approximately 12.5% of the sample identified as a sexual minority (n = 185). Psychological pain was significantly elevated among sexual minority (M = 27.89, SD = 11.76) versus heterosexual participants (M = 21.55, SD = 9.67), $t(219.55) = 6.992$, $p < .001$. Group averages for depression (Hedges' g = 0.60), psychological pain (Hedges' g = 0.64), and loneliness (Hedges' g = 0.34) were elevated for the sexual minority group. Sexual minority status remained a statistically significant predictor of psychological pain when accounting for depression and loneliness ($b = 2.18$, $SE = 0.58$, $p < .001$).

Conclusion. Our findings suggest that sexual minority individuals may be more likely to report elevated psychological pain compared to heterosexual peers. This study lays the groundwork for research examining antecedents and consequences of psychological pain among sexual minority young adults and developing more effective interventions to prevent suicide in this high-risk population.

Psychiatry

POSTER NUMBER:
228

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Peer Support and Psychological Well-being in Hematopoietic Stem Cell Transplantation Survivors

Investigators: D. Schaefer, E. Keane, A. Boardman, I. Larizza, H. Amonoo

Background : Survivors of hematopoietic stem cell transplantation (HSCT) often face significant psychological distress during recovery, which can reduce quality of life. Peer support—where patients provide emotional and practical guidance—has emerged as an important component of psychosocial care and may enhance psychological well-being. The Supporting Transplant Experiences with Peer Program (STEPP) is a five-session, structured, phone-based intervention where HSCT survivors offer support to others undergoing HSCT. However, little is known about how delivering peer support impacts the interventionists themselves.

Methods: HSCT survivors completed training to deliver the STEPP intervention. They participated in semi-structured qualitative interviews to explore their perspectives on STEPP's impact on their own well-being. The interviews examined interventionists' motivations, preferences, and challenges faced during STEPP. Interviews were transcribed, coded, and analyzed using framework-guided rapid analysis.

Results: Twenty HSCT survivors participated in the study (median age 63.5 years). Most interventionists were male (65%), Catholic Christian (30%), retired (60%), married (95%), identified as White (95%), and had at least a college degree (75%). Our findings indicate that peer support interventions benefit interventionists through reflective practices, cultivating positive thoughts and feelings, and facilitating emotional connections.

Conclusion: HSCT survivors serving as interventionists in peer support interventions, including STEPP, report that these interventions have the potential to enhance their psychological well-being. Therefore, peer support interventions should be refined and developed to optimally benefit both the interventionists and patients. Larger randomized clinical trials are needed to examine the efficacy of peer support interventions in improving health-related outcomes for patients undergoing HSCT.

POSTER NUMBER:
229

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Facilitation of Extinction Retention and Reconsolidation Blockade by IV Allopregnanolone in PTSD

Investigators: Rasmusson, G. Stalcup, S. Pineles, K. Brown

Here we show previous work and theoretical basis for a deep, mechanism-oriented rationale for the problems that contribute to risk, severity, chronicity and poor treatment response in PTSD. We also have pilot data demonstrating the role of Allopregnanolone in strengthening non-aversive memory consolidation.

Psychiatry

POSTER NUMBER:
230

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Delineating Network Integration and Segregation in the Pathophysiology of Functional Neurological Disorder

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Functional neurological disorder (FND) is a neuropsychiatric condition that is framed as a multi-network problem. Studies have generally focused on specific regions or connectivity features, under-characterizing the complexity of resting-state networks in FND pathophysiology. This study employed three complementary graph theory analyses to delineate the functional network architecture in FND: whole-brain weighted-degree, isocortical integration, and isocortical segregation, extracted from resting-state fMRI data collected from 178 participants (61 with mixed-FND; 58 psychiatric controls (PCs) matched on age, sex, depression, anxiety, and PTSD-severity; 59 age- and sex-matched healthy controls (HCs)). Analyses were adjusted for age, sex, and antidepressant use, and focused on differences between FND vs. PCs, with individual-subject maps normalized to HCs. Patients with FND-mixed vs. PCs exhibited increased weighted-degree in the right dorsal anterior cingulate and superior frontal gyrus, and the left inferior frontal gyrus and supplementary motor area. Integration analyses revealed increased between-network connectivity for somatomotor network areas, while segregation analyses revealed increased within-network connectivity for the dorsal anterior cingulate portion of the frontoparietal network. FND-motor and FND-seizure subtypes exhibited both shared and unique patterns, with individual connectivity values predominantly within the range of HCs. In post-hoc between-group analyses, findings remained significant adjusting for depression, anxiety and post-traumatic stress disorder severity, as well as for childhood maltreatment burden. Several between-group connectivity findings correlated with somatic symptom severity across FND and PC participants. This study provides novel mechanistic insights (i.e., increased somatomotor integration) and specificity regarding the neurobiology of FND, setting the stage for biologically-informed treatment development and large-scale replication

POSTER NUMBER:
231

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Resiliency in ME/CFS: A Multiphase Adaptation Project

Investigators: X. Zhu, S. Sethi, D. Felsenstein, D. H. Mehta, E. R. Park, D. L. Hall

Objective: Myalgic encephalomyelitis/chronic fatigue syndrome (ME/CFS) is a chronic medical condition that affects patients across various biopsychosocial factors. The Stress Management and Resiliency Training program (SMART-3RP) is an evidence-based multimodal mind-body group program with demonstrated efficacy in improving stress coping and resiliency in other populations. Yet, it lacks testing in ME/CFS. In this pilot study, we aim to explore the efficacy and feasibility of the SMART-3RP in ME/CFS.

Methods: In Phase 1, a single arm, prospective cohort of adults with ME/CFS (N=25) completed surveys pre-/post participation in virtual SMART-3RP sessions between Feb 2021 - Jul 2024. Patient-reported outcomes on stress coping (Measure of Current Status, Part A; MOCS-A) and resiliency (Current Experiences Scale; CES) pre-/post-program were analyzed using one-way ANOVAs to generate effect sizes ($\eta 2$). In Phase 2, we virtually interviewed 10 post-treatment participants to assess perceptions of feasibility and acceptability. Themes were identified through an iterative process using thematic analysis.

Results: Overall stress coping increased from pre- to post-program ($\eta 2=0.64$) on account of changes along MOCS-A subscales: Relaxation ($\eta 2=0.59$), Coping Confidence ($\eta 2=0.56$), Assertiveness ($\eta 2=0.41$), and Tension Awareness ($\eta 2=0.14$). Overall resiliency also increased from pre- to post-program ($\eta 2=0.37$), with a range of effects across CES subscales: Perceived Strengths ($\eta 2=0.50$), Appreciation for Life ($\eta 2=0.39$), Relating to Others ($\eta 2=0.21$), New Perspectives ($\eta 2=0.11$), Spiritual Connection ($\eta 2=0.03$), and Health Behaviors ($\eta 2=0.01$). Qualitative analyses suggest the eight-session virtual intervention was feasible and acceptable along group delivery, facilitation, and session content domains.

Conclusion: A virtual, multimodal mind-body intervention is promising for resiliency and coping in ME/CFS.

POSTER NUMBER:
232

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Comparison of Endovascular Therapy, Open Surgical Bypass, and Conduit Types for Index Treatment of Claudication in the Vascular Quality Initiative

Investigators: T. R. Bellomo, G. Jabbour , M. Manchella , S. K. Lella, S. Animilli , Y. Zhao , J. Lee , C. Y. Maximilian Png , B. Mulaney , B. Gaston , M. Eagleton , S. D. Srivastava , A. Dua, N. Zacharias

Background: Direct comparisons between endovascular and open surgical strategies for peripheral arterial disease (PAD) remain limited due to challenges in trial enrollment, anatomical variability, and lack of long-term follow-up. This study compares outcomes of index endovascular procedures versus open surgical bypass in claudicant PAD patients.

Methods: Data from 78,607 claudicants in the Vascular Quality Initiative (VQI) registry who underwent non-emergent femoropopliteal endovascular or open interventions were used in this study. The primary outcome was major amputation above the ankle. Cox proportional hazards models evaluated associations between procedure type, conduit type, and adverse events.

Results: Endovascular interventions had a significantly higher amputation risk at 30 days (HR 7.61, 95% CI 4.13-14.00, p<0.001), which remained elevated at one year (HR 5.13, 95% CI 4.09-6.44, p<0.001). Among open bypasses, prosthetic conduits had a higher amputation risk (HR 1.75, 95% CI 1.17-2.62, p<0.001) and lower primary patency (HR 0.88, 95% CI 0.83-0.94, p<0.001) at one year compared to great saphenous vein (GSV) conduits. Among GSV conduits, reversed GSV conduits had the highest amputation risk (HR 0.51, 95% CI 0.33-0.81, p=0.0024) compared to in situ and transposed GSV conduits (LRT p<0.001). Among prosthetic conduits, Dacron grafts trended toward higher amputation risk than polytetrafluoroethylene (PTFE) grafts (HR 3.41, 95% CI 1.01-11.56 vs. HR 1.58, 95% CI 1.28-1.94; LRT p=0.09).

Conclusions: Endovascular procedures were associated with higher rates of amputation and mortality at 30 days and one year compared to open surgical bypass. When feasible, transposed GSV conduits should be prioritized in surgical bypass to optimize outcomes.

POSTER NUMBER:
233

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Transcatheter Arterialization of Deep Veins: A novel approach to save limbs

Investigators: M. Boya, I. F. Cieri, A. A. Rodriguez Alvarez, S. Patel, A. Dua

Chronic limb-threatening Ischemia (CTLI) is the end stage of Peripheral Artery Disease (PAD). It often leads to amputation, causing severe morbidity and mortality among patients who have exhausted all the conventional treatment options. In these “no option patients”, a novel procedure known as Transcatheter Arterialization of Deep Veins (TADV) has recently emerged as a limb-saving alternative. While this procedure includes blocking smaller venous branches to direct arterial blood flow to the foot, this step’s necessity remains unproven.

Here we show that a simplified TADV approach without further venous branch coiling may achieve favorable outcomes. In our study of 26 patients, this streamlined technique resulted in an 87% limb salvage rate among survivors. The post-operative blood flow volume measurements demonstrated sustained venous system perfusion over three months, which maintained limb viability. Minor amputations were required in 26% of cases, all successfully managed with skin grafting. Secondary interventions were necessary only in six patients. Our results demonstrate that further venous branch blocking may be unnecessary in TADV. These findings suggest a potential for both improved procedural efficiency and reduced healthcare costs while maintaining successful limb salvage rates for CTLI patients.

Surgery

POSTER NUMBER:
234

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Reconstruction of Facial and Scalp Defects Using a Dermal Regeneration Template: A Retrospective Cohort Study

Investigators: M. R. Buta, A. K. Buckley, B. Bojovic

Background: Facial and scalp defects resulting from trauma, burns, or oncologic surgery often require skin grafts, tissue expansion, or flaps for wound coverage. Acellular dermal matrices have been increasingly utilized as an alternative to these approaches in select cases such as when autologous tissue is not suitable or is unavailable for reconstruction. This study presents our experience at a major academic hospital with single-stage reconstruction of facial and scalp defects using Integra bilayer dermal regeneration template.

Methods: A retrospective review of the electronic medical record was carried out on patients 18 years and older with facial or scalp defects resulting from trauma or oncologic surgery who underwent reconstruction with Integra Bilayer Wound Matrix by the senior surgeon between January 2016 and June 2024. Patient demographics, indication for reconstruction, wound characteristics, complications, and post-operative course were analyzed. A successful outcome was defined as >95% re-epithelialization after single-stage wound matrix application without the need for additional coverage procedures.

Results: We identified 49 patients (mean age: 65.7 years, SD: 14.1, range: 22.8-95.4) who underwent reconstruction at 50 different facial and scalp sites. The mean wound area treated was 19.4 cm2 (SD: 29.6, range: 1.8-150.0). The primary indication for surgery was oncologic reconstruction (n=45, 90%) followed by trauma (n=2, 4%) and exposed hardware (n=2, 4%). No patients required a locoregional flap due to incomplete re-epithelialization.

Conclusions: Integra can be safely and reliably used for single-stage reconstruction of select full-thickness facial and scalp defects resulting from trauma or oncologic surgery.

POSTER NUMBER:
235

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Rapamycin Treatment During Normothermic Machine Perfusion of Non-Utilized Human Livers Supports Level of Graft Function Required for Transplantation

Investigators: A. Cutrone, C. Taveras, M. Mojoudi, M. Taggart, O. S. Ozgur, M. Hassan, A. Lyon, A. Kharga, S. Raigani, K. Uygun, H. Yeh

Liver transplantation is limited by severe shortage in donor organs. Normothermic machine perfusion (NMP) of grafts allows for viability assessment and rehabilitation prior to transplantation. During NMP, recruitment of autophagy is associated with improved graft function, presumably through the support of cellular repair. To leverage the potential of this mechanism to rehabilitate donor livers, we evaluated the effect of treatment with rapamycin, a known activator of autophagy, during NMP of human livers. Here we show 6 human livers, not utilized for transplantation from donation after circulatory death, that underwent 12-hour perfusion, with introduction of either 10 nM or 50 nM rapamycin at t=0. Results were compared to 6 donor-matched control livers, representing either adequate graft function (AGF) or inadequate graft function (IGF) based on lactate clearance below 2.5 mmol/L in under 3 hours of NMP. 3 grafts receiving 50 nM rapamycin met this lactate clearance criteria for AGF, despite coming from donors of older age, higher donor risk index and experiencing longer cold ischemic time than IGF livers. Oxygen consumption, glucose metabolism, and bile production were also improved in 50 nM group when compared with IGF controls. Liver injury markers such as alanine and aspartate aminotransferase (ALT/AST) were decreased in 50 nM group when compared to all other groups, as were necrosis scores of tissue biopsies, suggesting preservation of viable tissue with rapamycin administration. Targeting of unregulated autophagy with rapamycin during NMP may represent a viable therapeutic intervention to rehabilitate injured donor livers.

POSTER NUMBER: **236**

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Selectin, Integrin, and Sialoadhesion Blockade in Ex Vivo Gene-Edited Pig Lung Perfusion with Human Blood

Investigators: M. Dufault, A. Sanatkar, S. Takemoto, V. Diaz, J. Schultz, M. Ma, S. De Taeye, J. Magnani, K. M. Whitworth, L. Burdorf, W. Eyestone, D. L. Ayares, Z. Habibabady, R. N. Pierson

Purpose: This study evaluates whether selectin and integrin blockade combined with donor organ gene editing (GE) strategies can reduce neutrophil and platelet sequestration, RBC damage, and inflammatory cytokine elaboration observed during ex-vivo pig lung perfusion with human blood.

Methods: Lungs with 3 carbohydrate antigen knockouts and 6 human transgenes (9GE) [GalKO.CMAHKO. β4GALKO.hCD46.hCD55.hTBM.hEPCR.hHO1.hCD47] +/- growth hormone receptor (GHR) (n=16) and GalKO lungs (n=8) were perfused with heparinized fresh human blood. Pigs received DDAVP to deplete vWF. The perfusate was treated with thromboxane synthase inhibitor (1-BIA) and histamine blockers; aGPIb Fab was added in some experiments. Treated perfusate received P and E selectin and integrin antagonists (rPSGL1.Fc, GMI1687, IB4), and porcine sialoadhesin blocker (mAb1F1) (9GE, n=8; GalKO, n=4). In 3 cases, 9GE+GHRKO (one +HLA-E) pigs received liposomal clodronate (LC) to deplete resident tissue macrophages, and the lung was perfused with combined treatment. Functional, blood, and tissue analyses were performed at set intervals.

Results: The combined treatment delayed but did not prevent neutrophil and platelet sequestration. MCP-1 levels were lowered, and RBC fragments and free Hgb were reduced in treated GalKO and 9GE lungs at 4hrs of perfusion compared to controls. LC-treated lungs showed delayed neutrophil sequestration during first 30 min, lower histamine levels (two cases), and reduced MCP-1 (one case) compared to other 9GE lungs.

Conclusion: Selectin, integrin, and sialoadhesion blockade is associated with delayed neutrophil and platelet sequestration and reduced hemolysis and cytokine levels by GE lungs. Pulmonary macrophage depletion with LC may enhance protection and further extend lung xenograft survival.

POSTER NUMBER: **237**

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Analytical and statistical validation of a high-throughput screening assay to establish methodology for discovery of new cryoprotective agents

Investigators: N. Gaby-Biegel, J. J. Jaskiewicz, A. Callahan-Muller, Z. Glover, R. D. Sandlin

The ability to preserve human organs through cryopreservation has huge implications for transplantation. Cryoprotective agents (CPAs) are used to minimize harmful ice formation during tissue freezing. CPA toxicity is a major limitation in cryopreservation. The discovery of new CPAs and formulation of low-toxicity CPA cocktails can be streamlined by use of high-throughput screening assays, which allow for rapid examination of a large chemical space. Here, we report the development of a high-throughput screening CPA toxicity assay, which was rigorously validated to ensure the production of high-quality datasets. The resulting assay, which consisted of a monolayer of T24 cells in a 96-well microtiter plate exposed to various CPA cocktails, was evaluated based on appropriate on-plate controls and statistical methods including calculation of the Z-factor, coefficient of variation, and plate drift. The reported assay exhibited a Z-factor of 0.75 and an intra-assay CV and drift of <20%, which indicated favorable assay quality. The assay was then used to perform a pilot screen of 587 unique CPA cocktails with concentrations ranging from 3.5-6 M. Each cocktail was tested with multiple replicates to characterize plate-to-plate and day-to-day variability of the assay (N=2-9, 2,352 total experiments). CPA cocktails tested at a concentration of 5 M were found to be most informative, where cell survival ranged from 2.8-87.3%, with a favorable hit rate of 1.7%, defined here as cell viability ≥80%. The validated assay is now being used in an ongoing experiment to screen for new CPAs.

POSTER NUMBER:
238

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Long-term Enhanced Subnormothermic Machine Perfusion of Discarded Human and Porcine Kidney Grafts

Investigators: M. Taggart, C. Taveras, A. Lyon, S. Sila Ozgur, A. Cutrone, M. Mojoudi

Purpose: Standard methods for preserving kidney grafts, including static cold storage (SCS) and hypothermic machine perfusion, often yield limited outcomes and high discard rates for donation after circulatory death (DCD) kidneys. This study evaluates the feasibility of extended subnormothermic machine perfusion (SNMP) to preserve graft viability and minimize ischemic injury. We compared DCD pig grafts stored for 24 hours with SNMP and SCS (n=3 each) and replicated the model with discarded human kidney grafts (n=3), with extended perfusion durations up to 33 hours.

Methods: DCD pig kidneys underwent 24 hours of pressure-driven SNMP. Discarded human kidneys were acquired from New England Donor Services and perfused for extended durations exceeding 24 hours using SNMP, including vasodilator and diuretic infusions. Porcine grafts underwent 2-hour blood reperfusion to simulate transplantation, comparing outcomes with time-matched SCS grafts. Human kidneys were perfused for up to 33 hours to assess preservation longevity under subnormothermic conditions.

Results: During 2-hour blood reperfusion, SNMP-preserved pig kidneys showed improved arterial resistance, creatinine clearance, and urine output compared to SCS controls. Human kidneys showed increasing resistance after 15 hours, though potassium levels remained stable, with gradual increases in urine production.

Conclusions: Here we show SNMP's potential for extended kidney preservation. The enhanced SNMP protocol improved porcine kidney function by maintaining oxygen and nutrient delivery. However, human grafts showed stable perfusion for only 15-18 hours, indicating the need for further optimization before clinical implementation.

Surgery

POSTER NUMBER:
239

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Fostering Growth Mindsets in Surgical Interns: A Multi-Institutional Pilot Intervention

Investigators: R. B. Tang, J. Warwick, D. Rothman, D. Chen, J. B. Greer, K. Baker, R. Phitayakorn, A. Guzzetta

Background: Growth mindset (GM), the belief that one's abilities can improve over time, is associated with enhanced learning, academic performance, and resilience. Most studies on GM in medical education to date are cross-sectional or exploratory. We describe the development, implementation, and evaluation of a longitudinal GM intervention for surgical interns.

Methods: This study occurs at two large general surgery residency programs during the 2024-25 academic year. We adapted an established GM intervention to the surgical residency context and held one interactive workshop at orientation and another at two months. GM was measured repeatedly via a validated questionnaire; differences and effect size were assessed with nonparametric tests. Free response comments on barriers to adopting GMs were inductively coded and thematically analyzed.

Results: Sixty-nine interns participated in the first workshop, and 36 (52.2%) participated in both. Over 85% somewhat or strongly agreed that the intervention was helpful. The mean GM score increased with large effect size from before to after the first workshop (36.2 to 38.6 out of 42, $Z=4.94$, $r=0.82$, $p<0.001$) but fell to baseline levels by the time of the second (34.8). Barriers included personal (ego and discomfort of learning new things), interpersonal (unsupportive culture including judgments from other team members), and structural factors (balancing learning with heavy clinical demands, performance evaluations).

Conclusions: A brief GM intervention is well-regarded by surgical interns and improves GM scores with large effect size. Learner-focused interventions may benefit from additional institutional efforts to address interpersonal and structural barriers which erode GM over time.

POSTER NUMBER:
240

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Randomized Controlled Trial of New Oral Anticoagulants Versus Warfarin for Post Cardiac Surgery Atrial Fibrillation: The NEWAF Trial

Investigators: A. Makarem, P. Moonsamy, Y. Zhao, D. C. Paneitz, S. Wolfe, D. A. D'Alessandro, A. S. Jassar, N. B. Langer, G. Tollis, M. A. Villaavicencio, S. I. Melnitchouk, J. P. Bloom, E. Michel, D. E. Cameron, A. Kreso, S. A. Rabi, O. Johnson-Akeju, T. M. Sundt, A. A. Osho

Background: Direct Oral Anticoagulants (DOACs) are noninferior to warfarin for stroke prevention in nonsurgical atrial fibrillation (AF) patients, with some studies suggesting a better safety profile. However, no randomized trials have compared DOACs to warfarin in cardiac surgery patients. We hypothesized that compared to warfarin, rivaroxaban will allow earlier hospital discharge and provide equally safe and efficacious prophylaxis against stroke.

Methods: In a pragmatic, prospective clinical trial, we randomized 100 patients with new-onset atrial fibrillation after cardiac surgery to receive rivaroxaban vs. warfarin. Patients were followed for 30 days after surgery and patient-reported outcomes were measured at 2 weeks post-discharge with the Perception of Anticoagulant Treatment Questionnaire and the EQ-5D-3L survey.

Results: Median hospital length of stay (days, IQR) was 7 (6–9) for rivaroxaban vs. 8 (6–9) for warfarin ($p=0.460$). Time from anticoagulation initiation to discharge was 2 (1–4) vs. 2 (1–3) days, respectively ($p=0.738$). No major bleeding, strokes, or thromboembolic events occurred. Minor bleeding events were 6% (rivaroxaban) vs. 2% (warfarin) ($p=0.617$). One pericardial effusion requiring drainage occurred in the rivaroxaban group ($p=1.000$). Patients taking rivaroxaban reported higher convenience scores ($p<0.001$) and better overall anticoagulation experience ($p=0.006$), though more rivaroxaban users reported mobility issues (42.2% vs. 18.6%, $p=0.021$).

Conclusion: In patients with new atrial fibrillation after cardiac surgery, rivaroxaban was as effective as warfarin in preventing stroke, without increased risk of bleeding. There was no significant between-group difference in hospital length of stay. Patients preferred rivaroxaban for its convenience and better overall experience, supporting its use in shared decision-making.

POSTER NUMBER:
241

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Modulation of NK Cell-Mediated Immune Responses by HLA-E-Expressing Genetically Modified Porcine Endothelial Cells

Investigators: J. A. Schulz, Z. Habibabady, A. Sanatkar, V. Diaz, M. Dufault, K. Kuravi, M. Kokkanaki, S. Butler, R. N. Pierson III

PURPOSE OF THE STUDY: Natural Killer cells are a major barrier to xenotransplantation. HLA-E binds the inhibitory CD94/NKG2A receptor on human NK cells (hNK), suppressing their activation. This study evaluates the impact of HLA-E expression on genetically engineered (GE) porcine aortic endothelial cells (PAECs) in reducing hNK-mediated cytotoxicity and degranulation.

METHODS: hNK were isolated and cultured with IL-2. GE PAECs included Gal-knockout (GalKO/WT) cells, 10GE triple-knockout (GalKO, β4GalKO, CMAHKO) cells with human genes (hCD46, hCD55, hTBM, hEPCR, hHO1, hCD47, GHR knockout), and HLA-E-expressing 11GE cells (10GE+HLA-E=11GE cells). Cytotoxicity was measured via an LDH release assay and degranulation was quantified by CD107a flow cytometry after a co-culture with hNK. To probe the HLA-E pathway, an anti-CD94 blocking antibody was added to hNK before incubation with 11GE. A co-culture fluorescent microscopy assay using DiOC6 (live cells) and PI (dead cells) was performed to visualize hNK-mediated cytotoxicity.

RESULTS: HLA-E expression on GE PAECs significantly reduced hNK-mediated cytotoxicity (fold change 0.63, n=4, p=0.0187) compared to GalKO/WT (n=4), whereas 10GE showed no significant reduction (fold change 0.83, n=3, p=0.3294). GalKO induced 25.07% degranulation (n=2), 10GE cells 20.70%, and 11GE cells 15.65% (n=2). Blocking CD94 on hNK reversed HLA-E's protective effect, increasing cytotoxicity and degranulation. The proportion of PI-positive cells was lower in co-cultures with HLA-E-expressing PAECs (36%, n=5) versus GalKO (66%, n=5) and 10GE (54%, n=4).

CONCLUSIONS: HLA-E expression on GE PAECs markedly reduces hNK cell-mediated immune reaction via CD94, highlighting its potential in xenotransplantation. Ongoing experiments include repeating these experiments on Baboon NK cells.

POSTER NUMBER:
242

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A Pilot Study of Microcolumn Skin Grafting in Full-thickness Burns

Investigators: M. R. Buta, M. D. Supple, S. A. Hickey, J. S. Friedstat, J. T. Schulz, E. A. Bittner, J. M. Goverman

Background: The technique of micro skin tissue column (MSTC) grafting was developed as an alternative to split-thickness skin grafts (STSGs) and full-thickness skin grafts (FTSGs) for acute and chronic skin wounds This pilot study evaluated the feasibility of treating third-degree, full-thickness burn wounds with both STSGs and MSTCs. Donor sites for both grafting techniques were also assessed.

Methods: Patients aged ≥18 years with ≤60% total body surface area (TBSA) third-degree, full-thickness burns were enrolled. One 2.5 x 2.5 cm2 wound area was treated in each subject, with the remaining portion of the wound used as an internal control. The target wound was treated with MSTCs + STSG while the control site was treated with STSG. Patients were followed for up to nine months after wound closure. Primary endpoints included re-epithelialization rate (RER), scarring (Vancouver Scar Scale, Patient and Observer Scar Assessment Scale), and donor site pain (visual analogue scale).

Results: Ten patients were enrolled. Overall, MSTC donor sites were less painful, epithelialized faster, and resulted in improved POSAS and VSS scores than STSG donor sites. For all endpoints, there were no differences in the target wounds treated with or without MSTCs.

Conclusion: Intraoperative MSTC grafting is feasible and results in minimal donor site morbidity. This pilot study was unable to demonstrate enhanced wound healing or improved scar formation when MSTCs were applied simultaneously with STSGs to burn wounds. Larger clinical studies are needed to assess the utility of MSTCs in conjunction with STSGs.

POSTER NUMBER:
243

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Early Reporting of Transplant Rejection: Genetically Engineered 'Smart-Organs' Featuring Diagnostic Capabilities

Investigators: I. Filz von Reiterdank, R. Bento, A. T. Dinicu, C. Taveras, M. Hassan, M. Mojoudi, H. Chen, B. W. Ellis, G. Wojtkiewicz, R. Weissleder, B. E. Uygun, C. L. Cetrulo Jr, J. H. Coert, A. B. Mink van der Molen, B. Parekkadan, K. Uygun

Background: Early detection of organ transplant rejection is hindered by limitations of existing diagnostic tools. Current blood tests lack sensitivity and specificity, while biopsies remain invasive. To address these challenges, this study explores a novel approach that combines gene therapy and machine perfusion to enable long-term genetic modification and, subsequently, non-invasive and early detection of rejection in transplanted organs.

Methods: Vascularized composite allografts (VCA) were genetically modified ex vivo using lentiviral vectors as gene delivery systems during ex vivo machine perfusion. To show long-term genetic modification, a constitutive (EF1a) promoter was used in a non-rejection transplant model. Second, in a partial mismatch transplant model, VCAs were transduced using an inflammation-responsive element designed to detect rejection events, releasing a blood-based biomarker, Gaussia Luciferase (GLuc).

Results: Genetically modified VCAs demonstrated transgene expression for over 350 days in the non-rejection model. The inflammation-responsive system enabled detection of rejection by in vivo bioluminescence six days before histological evidence of rejection. GLuc was reliably measurable in the bloodstream as a biomarker at the beginning of rejection episodes. Under immunosuppression, rejection animals showed GLuc levels comparable to controls.

Conclusion: This study provides the first evidence that genetically modifying organs during machine perfusion can enable long-term transgene expression and improve diagnostic capabilities in organ transplantation. Integration of a synthetic promoter and inflammation-responsive elements facilitated earlier and non-invasive detection rejection, with potential implications for improving long-term graft survival and enhancing transplant management strategies. This approach marks a significant advancement in leveraging gene therapy for clinical transplantation.

POSTER NUMBER:
244

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AAV-bNAb Vectored ImmunoTherapy as a functional cure of HIV-1 in humanized mice

Investigators: N. M. Galvez, A. D. Nitido, S. B. Yoo, Y. Cao, C. E. D, A. B. Balazs

HIV persists as a pandemic despite the effectiveness of combination antiretroviral therapy (cART). cART treatment interruption results in the swift reemergence of the virus from latent reservoirs and viral pathogenicity. Broadly neutralizing antibodies (bNAbs) have been discovered which have the capacity to neutralize across diverse HIV isolates. They have been shown to prevent and treat HIV infection clinically, but their widespread implementation is undermined by the need for repeated administration and the emergence of viral strains capable of escaping the antibody. A single administration of an adeno-associated viral (AAV) vector encoding bNAb results in long-lived expression of high titers of antibodies. This approach is known to prevent HIV infection in different animal models, but its efficacy against established infections requires further characterization. Here we show that monotherapy with AAV-VRC07 results in long-term suppression of HIV in half of the mice, which was not observed for experiments with other viral strains or other bNAbs. Interestingly, traditional breadth and potency metrics were poor predictors of therapeutic outcome; instead, the efficacy of bNAbs delivered as Vectored ImmunoTherapy (VIT) depended on the trade-off between fitness cost and neutralization resistance of escape mutations, a relationship we termed “escapability”. By levering the escapability of each bNAb against HIV, we were able to determine a combination of bNAbs capable of consistently suppressing HIV infection. Our data suggests that the use of AAV-bNAbs is a promising therapeutic approach and may form the basis of a functional cure against HIV.

POSTER NUMBER:
245

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Developing Viability Protocols for Long-Term Culture of Skin Grafts

Investigators: E. S. Herman, A. T. Dinicu, I. Filz von Reiterdank, R. Bento, A. B. Mink van der Molen, J. H. Coert, B. Parekkadan, K. Uygun

Introduction: Burn injuries, particularly in pediatric patients, present a major global health burden with significant mortality rates that increase with burn size. Reconstructive options for large body surface area burns are limited due to donor site scarcity. The alternative, allogeneic grafts, are typically rejected within 2–3 weeks. Literature on long-term ex vivo skin graft culture is limited, therefore, this study aims to bridge this gap by optimizing long-term ex vivo culture conditions to maintain skin viability, which can be used to study treatments focused on improving pediatric burn reconstruction.

Methods: Skin grafts (800 µm, Yorkshire pigs) were divided into two groups: fresh (n=3), and cryodamaged skin grafts (n=2). Cryodamaged grafts were stored at -80°C for 3 weeks. Grafts were incubated in Dulbecco’s Modified Eagle Medium at 37°C 10% CO2. In supernatant, glucose consumption, lactate, and potassium levels were assessed on day 1 and 3.

Results: Fresh grafts demonstrated significantly higher glucose consumption and lactate production compared to cryodamaged grafts, with both metrics decreasing by day 3, indicating metabolic activity decline (Fig 1). Potassium levels also showed a slight decrease in fresh grafts by day 3 (Fig1).

Conclusions: These findings suggest ex vivo skin viability can be maintained for 3 days. To validate viability assessments, skin grafts will be transplanted into nude mice to correlate in vitro parameters with in vivo survival. This work establishes a foundation for future studies leveraging long-term skin graft culture, including gene editing, recellularization, and investigating ex vivo treatments to improve pediatric burn reconstruction outcomes.

Translational Medicine & Experimental Therapeutics

POSTER NUMBER:
246

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Novel Molecular Approaches to Rapidly Characterize and Engineer Precise CRISPR Base Editors

Investigators: E. M. King, R. A. Silverstein, M. A. Fallon, B. P. Kleinstiver

Genetic mutations cause a wide range of human diseases, with more than 6,000 disorders caused by single mutations. Base editors (BE) are a highly efficient CRISPR-based technology that can programmably install single-nucleotide corrections in DNA, enabling modeling or correction of disease-causing genetic variants. BEs have already been proven safe and effective in human patients. Unfortunately, BEs often introduce unwanted edits adjacent to the target nucleotide (so-called 'bystander edits'). To enhance on-target correction while minimizing unwanted bystander editing with BEs, protein engineering methods can in principle be utilized to develop BEs with increased precision, efficiency, or sequence preferences. However, traditional protein engineering workflows all face a common bottleneck: following the engineering campaign, the number of enzymes that can be comprehensively characterized is extremely limited, motivating a need for new assays that permit a global assessment of orders of magnitude more enzymes. To overcome these challenges, we have developed a method that enables the rapid and parallelized screening and characterization of hundreds BE proteins on hundreds of putative target sites. We have utilized this assay to generate comprehensive datasets related to enzyme kinetics, edit types, and sequence preferences hundreds of different BEs, in a simple assay that can be parallelized to profile 96+ enzymes at a time. Together, our work permits the exploration and engineering of BEs at formerly cost and time prohibitive scale, and we have leveraged the assay to identify novel BEs that are effective and safe for therapeutic applications.

Translational Medicine & Experimental Therapeutics

POSTER NUMBER:
247

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Phosphoproteomic analysis identifies mechanisms of resistance to mutant-selective KRAS inhibitors in KRAS-mutant pancreatic cancer

Investigators: Q. Lin, B. Song, A. Morales, F. M. White, R. B. Corcoran, GI

Clinical outcomes for pancreatic ductal adenocarcinoma (PDAC) patients remain dismal, with the lowest 5-year survival rate among prevalent cancers. KRAS mutations, present in 90% of PDAC cases, have recently been reconsidered as 'druggable' and have shown clinical promise. KRASG12C inhibitors (KRASiG12C) have demonstrated initial clinical responses in PDAC, and inhibitors targeting KRASG12D, the most common KRAS mutation in PDAC, are currently undergoing clinical trials at MGH. However, resistance to KRASiG12D remains a clinical challenge, necessitating a deeper mechanistic understanding and the development of novel therapeutic strategies.

Using drug combination screening and phosphorproteomic approaches, MAPK-dependent signaling rebound was identified as a major mechanism of adaptive resistance to KRAS inhibition, which was mediated by FGFR or EGFR in a cell-state-dependent manner. Notably, combining KRASG12D inhibitors with pan-RAS inhibitors, which target both wild-type and mutant RAS, completely abrogated MAPK signaling and stabilized tumor progression and significantly improved animal survival in PDAC tumor models resistant to single-agent therapies, regardless of cell states. This result suggested a heterogeneous pro-survival dependency converging on wild-type RAS.

Furthermore, temporal phosphoproteomic analysis across six PDAC models identified that SRC-family protein tyrosine kinases (SFKs) were the most upregulated following KRASG12D inhibition, with increased substrate phosphorylation activity. Importantly, co-inhibition of SFK and KRAS killed ~90% tumor cells by suppressing MAPK rebound and other mechanisms in highly resistant models with marginal suppression by single-agents. These findings highlighted a critical role of SFKs in resistance to KRAS inhibition and support an ongoing clinical trial investigating the combination of FAK inhibitors with KRAS inhibitors.

Translational Medicine & Experimental Therapeutics

POSTER NUMBER: **248**

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CANaspire Gene Therapy Trial: A Targeted Approach to Slowing Disease Progression in Pediatric Patients with Canavan Disease

Investigators: F. Eichler, R. Thompson, M. Nagy, B. Kinane, D. Oje, G. Laforet, A. Fay, P. Harmatz, E. Mallack, C. Burton, E. Townsend, M. Kiefer, B. Leiro, R. Williams, A. Shaywitz, A. Bley, C. Becker, Y. Li, R. Saxena, H. McLaughlin, Center for Rare Neurological Diseases at MGH

Canavan disease is a rare and fatal neurodegenerative disorder caused by mutations in the ASPA gene, leading to the toxic accumulation of N-acetylaspartic acid (NAA) and severe white matter degeneration. This international, multi-center study evaluates the safety and efficacy of adeno-associated virus (AAV)-mediated gene therapy as a potential treatment for affected children. Pediatric patients under 30 months receive glucocorticoid prophylaxis for immunosuppression before a single intravenous dose of recombinant AAV9 (rAAV9) carrying an ASPA transgene (BBP-812). Patients then undergo comprehensive neurological, biochemical, and caregiver-reported assessments over a five-year follow-up period.

To date, 17 patients have been enrolled in the study, with 10 currently receiving treatment at MGH. Six demonstrated high tolerability at the low dose of BBP-812, with few treatment-emergent adverse events, supporting expansion to a higher dose. Efficacy measures—including NAA levels in urine and cerebrospinal fluid, adverse event monitoring, brain MRI, and motor function assessments—have shown promising outcomes. Participants exhibited rapid and sustained NAA reductions, with strong correlations between urine and brain levels, as well as MRI evidence of white matter improvement and new myelination. Motor function was stabilized or improved, in some cases surpassing typical disease expectations.

These findings suggest that AAV-mediated gene therapy holds significant promise in altering the trajectory of Canavan disease. Further research will refine dosing strategies, assess long-term benefits, and explore broader applications in pediatric neurogenetic disorders.

POSTER NUMBER: **249**

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Developing liquid biopsy approaches to monitor muscle-specific damage in Duchenne Muscular Dystrophy

Investigators: E. E. Rodriguez, J. Cheam, U. Paithankar, M. Garcia Contreras, B. Kaszala, M. Song, E. Biederstedt, S. Das, Y. Kim, S. Stott, M. Rengarajan

Duchenne muscular dystrophy (DMD) is a fatal pediatric neuromuscular disease marked by progressive muscle loss, leading to loss of ambulation during childhood and death from heart failure in early adulthood. DMD is caused by mutations in the DMD gene which encodes the protein dystrophin, an essential regulator of heart and skeletal muscle function and recovery. Therapeutic development in DMD has been stymied by the lack of reliable non-invasive markers of progressive tissue damage.

We aim to develop liquid biopsy approaches that enable non-invasive monitoring of heart and skeletal muscle damage in DMD; our goal is to develop tools to monitor disease progression and rapidly determine the efficacy of therapeutic interventions. Here, we propose an approach to analyze extracellular vesicles (EVs) derived from cardiomyocytes (CM) or skeletal myocytes (SKM). We aim to leverage tissue-specific EVs to non-invasively examine tissue-specific gene and protein expression. As an initial test case, we will examine tissue-specific expression and durability of dystrophin-like transgenes delivered to patients with DMD who receive gene therapy.

POSTER NUMBER:
250

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Effects of the Ghrelin Agonist Relamorelin on Food Reward and Cognitive Control in Women with Anorexia Nervosa: A Preliminary fMRI Study

Investigators: A. Shreekumar, P. K. Fazeli, J. J. Thomas, F. Plessow, T. Deckersbach, A. Klibanski, K. T. Eddy, E. A. Lawson, L. M. Holsen

Anorexia Nervosa (AN) is characterized by hypoactivation of food reward circuitry and hyperactivation of cognitive control brain regions. It is also marked by ghrelin resistance, where high levels of the hunger-related hormone fail to stimulate food intake. We hypothesized that administering a ghrelin agonist, relamorelin (RM-131), would overcome this resistance, increasing activation in food motivation regions and decreasing activation in cognitive control to normalize appetite signaling in women with AN.

In a randomized, double-blinded trial, five women (age: 28.9 ± 2.4 y) with AN received a 100 µg dose of RM-131 (n=2) or placebo (n=3) for four weeks. Before and after administration, participants viewed food- and non-food images during fMRI scanning. Scan data were collected pre- and post-meal.

There was a significant Group × Time interaction in premeal activation to food (vs. non-food) stimuli driven by increased activation of reward-related regions in the RM-131 group: nucleus accumbens (puncorr=0.047, cluster size (ke)=1), caudate (puncorr=0.007, ke=25), orbitofrontal cortex (puncorr=0.002, ke=10), insula (puncorr=0.005, ke=4), amygdala (puncorr=0.03, ke=5), hippocampus (puncorr=0.005, ke=10). There was a Group × Time interaction in the dorsolateral prefrontal cortex (DLPFC; puncorr=0.000, ke=419), also driven by increased premeal activation in the RM-131 group.

Findings suggest that ghrelin agonists may enhance food motivation by increasing activation in reward-related brain regions, consistent with the proposed mechanism of overcoming ghrelin resistance. Increased activation in the DLPFC suggests complex interactions between cognitive control and reward processing. Larger ghrelin agonist trials with behavioral measures are warranted to assess efficacy and safety.

POSTER NUMBER:
251

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Harnessing the power of the Proneural Gene Ascl1: A Gene Therapy Approach for Treating Hirschsprung Disease (HSCR)

Investigators: F. Vipin, R. Hotta, R. Stavely, A. Goldstein

The enteric nervous system (ENS) controls vital functions including motility, secretion and blood flow within the gut. Defects in the ENS cause serious congenital diseases, such as Hirschsprung disease (HSCR), which affects 1 in 5000 children and is characterized by the absence of ganglion cells along a variable length of distal bowel. HSCR is due to a defect in colonization of neural crest-derived cells during gut development. The nonfunctional aganglionic region leads to bowel obstruction and treatment involves surgical removal of this portion. While the surgical approach is pivotal, the patients still face GI problems such as constipation and enterocolitis throughout their life. While the aganglionic region is devoid of intrinsic enteric neurons, extrinsic derived hypertrophic neural fibers are present in that segment. These hypertrophic nerve fibers harbor Schwann cells that have neurogenic potential and can be harnessed to replace the missing neurons. AAV-mediated gene therapy offers the potential to induce neurogenesis in the aganglionic region and thereby ameliorate the functional deficits in HSCR. Using single cell RNA sequencing, we found that a neurogenic population of intraganglionic glial cells is missing in Ednrb knock-out mice, a model of HSCR. These missing glial cells normally express high levels of the proneural transcription factor, Ascl1 (Mash1), which is required for neuronal differentiation during ENS development. In this study we explore Ascl1 gene therapy to induce neurogenesis in Schwann cells of the aganglionic HSCR colon, achieving AAV-mediated Ascl1 expression in enteric glia, with implications for restoring neuronal innervation as a potential HSCR treatment.

POSTER NUMBER:
252

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Hormonal Intrauterine Devices Associated with Lower Long-Term Melasma Risk Compared to Combined and Progestin-Only Oral Contraceptives

Investigators: D. Cheng, A. Gaurav, D. Xiang, H. Ji, D. Hirsh, S. Chen, A. Mostaghimi, K. Ma, N. Theodosakis

This study investigated melasma risk in users of hormonal intrauterine devices (hIUDs), progestin-only contraceptives (POCs), and combined oral contraceptives (COCs), addressing the underexplored associations of hIUDs and POCs with melasma. We conducted a cohort study using TriNetX (95 healthcare organizations), identifying patients aged 18-52 with menorrhagia treated with hormonal contraceptives (2001-2024), stratified into COC, POC, hIUD, and hormone-unprescribed control cohorts. Propensity score matching controlled for demographics, medications, procedures, and comorbidities. Over 1 year, no melasma risk difference was observed among COCs (RR: 1.50; 95% CI: 0.80-2.83), POCs (RR: 1.00; 95% CI: 0.42-2.40), hIUDs (RR: 1.00; 95% CI: 0.42-2.41), and controls. Over 3 years, COCs showed increased risk (RR: 2.42; 95% CI: 1.57-3.72), while POCs (RR: 1.80; 95% CI: 0.96-3.38) and hIUDs (RR: 1.31; 95% CI: 0.64-2.70) did not. At 5 years, increased risk was observed for COCs (RR: 2.68; 95% CI: 1.86-3.85) and POCs (RR: 1.95; 95% CI: 1.10-3.43), but not hIUDs (RR: 1.59; 95% CI: 0.87-2.92). Findings indicated no melasma risk for hIUDS, whereas there was significantly increased risk at 3 and 5 years for COCs and at 5 years for POCs, suggesting hIUDs may be the better option for chronic dyspigmentation concerns. Our findings suggest melasma risk may be proportional to systemic hormone absorption. Limitations include inability to assess treatment adherence or misdiagnosis, mitigated by requiring at least two prescription codes for oral contraceptive inclusion and using previously validated diagnostic codes. Future studies may explore the potential benefit of switching from oral contraceptives to hIUDs for melasma management.

POSTER NUMBER:
253

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Outcomes after a prior term delivery affected by an admission for preterm labor

Investigators: A. Delgado, K. E. James, M. A. Clapp, M. D. Soffer

Preterm birth (PTB) poses significant maternal and neonatal risks. It is unknown if patients presenting with symptoms of preterm labor that deliver at term are at higher risk for PTB in subsequent pregnancies. Therefore, we aimed to characterize subsequent singleton pregnancy outcomes among women with a prior singleton term delivery complicated by antepartum admissions due to concerns for preterm labor. A retrospective cohort study of patients who: 1) had a term singleton delivery after an inpatient admission due to concern for preterm labor, and 2) a subsequent singleton pregnancy within the analysis time between 2016 to 2023 was completed. Data was abstracted and verified with chart review for 80 patients. Index and subsequent pregnancy characteristics were compared. The average gestational age at delivery was 38.8 (SD 1.3) weeks in the index pregnancy. Eight (10%) patients had a PTB in their subsequent pregnancies. PTB in subsequent pregnancies was associated with significantly more admissions and triage evaluations (100% vs 26%, $p<0.001$) and betamethasone administration for fetal lung maturity (62% vs. 8%, $p<0.001$). We saw no differences cerclage placement or vaginal progesterone use for prevention of preterm birth. We found 10% of women with term singleton births affected by antepartum admissions for preterm labor have subsequent pregnancies affected by PTB. While similar to the baseline risk, this is higher than the previously reported risk of PTB following a term delivery. These findings highlight an area of future research regarding the risk factors for PTB and may guide providers with respect to patient counseling.

POSTER NUMBER:
254

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Maternal substance uses and immune activation: a pathway to adverse neurodevelopmental outcomes

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Problem: Substance use in pregnancy is a significant public health crisis with transgenerational impact. Maternal substance use, most commonly including opioids, cannabis, and alcohol, is associated with adverse offspring neurodevelopment, including risk for autism spectrum disorder, attention deficit hyperactivity disorder, and cognitive and neuropsychiatric outcomes. Yet, the underlying mechanisms by which prenatal exposures to these substances result in long-term offspring neurodevelopmental morbidity remain largely unknown. We sought to evaluate maternal and cord blood immune activation in substance use by profiling maternal and cord blood peripheral blood mononuclear cells PBMC with flow cytometry.

Method: 16 pregnancies with maternal substance use were each matched controls for gestational age at blood collection, fetal sex, and maternal pre-pregnancy obesity status. Maternal and cord blood PBMC samples were profiled using flow cytometry to evaluate shifts in T cell subset frequency, phenotype, and activation level associated with substance use in pregnancy.

Conclusion: Evaluation of lymphocyte subset frequency and activation level demonstrated that substance use in pregnancy is associated with immune dysregulation, including increased pro-inflammatory responses. These proof-of-principle data will inform the same experiments we perform on maternal and cord blood PBMC and placentas from a subset of 400 participants in the large national HEALthy Brain Child Development (HBCD) consortium study. These studies will enable us to link the degree of maternal immune activation in substance use with offspring neurodevelopmental phenotyping. We anticipate that these data will help identify a common pathway by which diverse maternal substance use may result in adverse neurodevelopmental outcomes in children.

POSTER NUMBER:
255

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The impact of oocyte donation on placental pathology among singleton livebirths conceived following in-vitro fertilization (IVF)

Investigators: M. Kavelidou, A. M. Sassin, E. E. Minis, I. Dimitriadis, K. E. James, C. L. Bormann, D. J. Roberts, I. Souter

Pregnancies conceived through oocyte donation carry a higher risk of adverse perinatal outcomes compared to autologous oocyte conceptions, possibly due to an immune-mediated maternal response to embryo-derived antigens. With shifting societal norms and increasing parental age, oocyte donation is becoming more common, making it crucial to better understand maternal adaptation and the pregnancy complications mediated by altered placentation.

This retrospective study included 743 IVF-conceived singleton live births from a single fertility center (2004–2022). Placental pathology was compared between donor(n=49) and autologous(n=694) oocyte pregnancies (the latter restricted to patients<35years to minimize confounding by oocyte age.) Placental pathology was classified into anatomic, inflammatory, infectious, and vascular abnormalities by a blinded expert pathologist. Parametric/non parametric tests were used as appropriate. Generalised estimating equations were employed to calculate adjusted odds ratios(adjOR) and 95%CI after controlling for potential confounders, (autologous oocyte group:reference).

Donor oocyte recipients vs. patients conceiving with autologous oocytes were older, with lower AMH, and higher BMI[mean(SD): 40.9(5.0) vs.32.2(2.5)years, p<0.01; 0.4(0.6) vs.4.6(4.6)ng/ml, p<0.01; 32.7(4.9) vs.24.5(4.6)kg/m2, p<0.001; respectively].The commonest diagnosis among the former group was diminished ovarian reserve(89.6%), while in the latter was male factor(47.2%). 30.6%, and 69.4% of the placentas originated from fresh and frozen embryo transfers, respectively. AdjOR (95%CI) showed significantly higher anatomic[1.49(1.30-1.72), p<0.001], inflammatory[1.80(1.52-2.14), p<0.001], infectious[1.62(1.38-1.91), p<0.001], and vascular[1.21(1.10-1.33), p<0.001] abnormalities in the donor vs. autologous oocyte conceptions.

Placentas from oocyte-donor pregnancies exhibited higher rates of abnormalities across the entire placental pathology spectrum, highlighting the need for further research into maternal-fetal interaction mechanisms, to improve clinical management, donor selection criteria, and immunomodulatory strategies among these pregnancies.

POSTER NUMBER:
256

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A Pilot Study Evaluating Associations Between Continuous Glucose Monitoring Metrics in Pregnancy and Postpartum A1c

Investigators: C. F. Michalopoulos, R. L. Azevedo, S. Hsu, A. Medina Baez, E. A. Rosenberg, C. E. Powe

Pregnant individuals with gestational diabetes (GDM) are at risk for future type 2 diabetes (T2D). GDM screening is performed routinely at 24-28 weeks' gestation via oral glucose tolerance test (OGTT). Individuals with GDM undergo another OGTT at 4-12 weeks' postpartum for T2D risk stratification, but completion rates are <50%. Continuous glucose monitoring (CGM) is increasingly used in pregnancy. If CGM during pregnancy can accurately predict future T2D among people with GDM, the postpartum OGTT may be unnecessary. In this pilot study, we evaluated the willingness of participants from a previous pregnancy study to return for a visit at >6 months postpartum and explored associations of third trimester CGM metrics (mean glucose, % time in pregnancy range 63-140 mg/dl [pTIR], % time >140 mg/dl, % time >120 mg/dl, and variability measured by coefficient of variation [CV]) with postpartum hemoglobin A1c (HbA1c) levels using linear regression models with adjustment for body mass index. Analyses were conducted with and without a potentially influential outlier. Of 13 participants contacted, 10 returned for a study visit at ~20 months postpartum. Participants on glucose-lowering medication (n=2) were excluded from analyses. Higher glucose variability (CV) in the third trimester was associated with higher postpartum HbA1c (β=0.07, p=0.004 without outlier, β= 0.07, p=0.03 with outlier). Lower pTIR was associated with higher postpartum HbA1c (β=-0.06, p=0.008 without outlier). This study demonstrates the willingness of past participants with GDM to return for follow-up studies. Future larger studies should examine the ability of CGM data from pregnancy to predict future T2D.

POSTER NUMBER:
257

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Investigating Diverse Unsaturated Long Chain Fatty Acid Metabolites as a Novel Approach to Bacterial Vaginosis Treatment

Investigators: D. Wang, M. Zhu, B. Read

Bacterial vaginosis (BV), a common gynecologic disorder, affects up to 58% of uterus-havers worldwide and is clinically characterized by increased watery discharge, odor, and mucosal inflammation. BV is microbiologically characterized by an overabundance of diverse anaerobes and a paucity of lactobacilli and is further associated with negative health outcomes of miscarriage, preterm birth, cervical dysplasia, infertility, and sexually transmitted infections including human immunodeficiency virus (HIV) risk. In contrast, Lactobacillus-dominated cervicovaginal microbiomes – most notably L. crispatus – have the most beneficial health associations. However, microbiomes dominated by another common Lactobacillus species, L. iners, is associated with BV recurrence. First-line BV treatment, metronidazole (MTZ), often results in high recurrence rates (>50%), in part because MTZ promotes microbial dominance by L. iners rather than the more health-associated L. crispatus. Thus, alternative strategies to promote the beneficial growth of L. crispatus while simultaneously inhibiting L. iners and other BV-associated anaerobes are needed. Here we show that unsaturated long chain fatty acids (uLCFAs), such as oleic acid, palmitoleic acid, linoleic acid and more, have been demonstrated to inhibit L. iners and promote L. crispatus. We set out to evaluate the effects of more diverse uLCFA metabolites on L. crispatus, L. iners, and diverse BV-associated species to further explore the potential of this class of metabolites in improving existing BV treatment. We further characterize the safety of these uLCFAs in vitro and demonstrate a stable shift toward a health-associated state in a mock BV community.