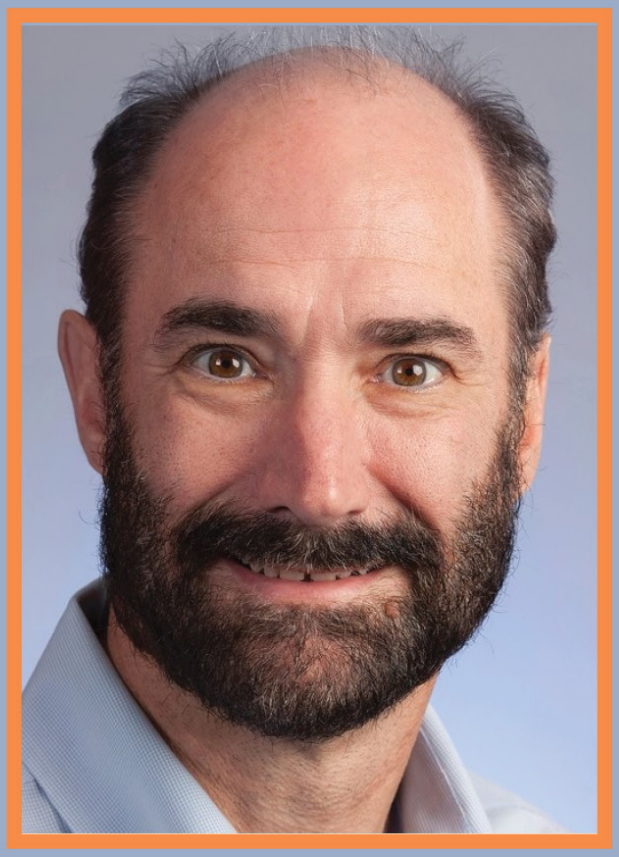
Johns Hopkins Department of Medicine & Whiting School of Engineering

RESEARCH RETREAT

presents



KEYNOTE SPEAKER

Michael Snyder, PhD
Chair, Department of Genetics
Director, Center for Genomics and Personalized Medicine
Stanford University School of Medicine

SPOTLIGHT ON RESEARCH

Featuring Select Faculty and Trainees from the Johns Hopkins Department of Medicine & Whiting School of Engineering

POSTER SESSION

DATE

Friday, February 9, 2024
8:30 a.m.- 2:15 p.m.

JOHNS HOPKINS SCHOOL of MEDICINE

JOHNS HOPKINS WHITING SCHOOL of ENGINEERING

Welcome to the Johns Hopkins 2024 Department Of Medicine/Whiting School of Engineering Research Retreat

The Department of Medicine and Whiting School of Engineering Research Retreat is about connections. Connections among researchers in both schools, connections between mentors and mentees and connections between leadership and the adventurous researchers that elevate the discovery community.

Our annual retreat is the largest forum for the presentation of research by Department of Medicine and Whiting School of Engineering faculty, staff and trainees. The retreat has a long-standing history in the Department of Medicine but has seen its greatest success since joining forces with the Whiting School of Engineering in 2018.

This year, we welcome Keynote Speaker Michael Snyder, PhD, chair of the Department of Genetics and director of the Center for Genomics and Personalized Medicine at the Stanford University School of Medicine.

Once again, we are thrilled that our keynote address, spotlight on research talks and award presentations will happen in conjunction with the poster session that is known to fill Turner Concourse with bold and creative research initiatives at Johns Hopkins. We hope the event will fuel new collaborations and capitalize on the investigative strengths of each enterprise.

Enjoy the connections!

Nadia N. Hansel, MD, MPH
Interim Director, Department of Medicine

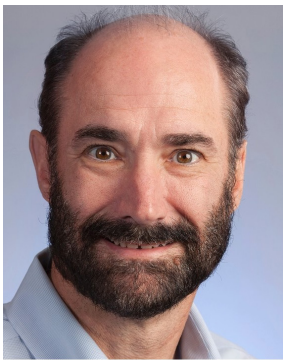
Interim Physician-in-Chief, Johns Hopkins Hospital

T.E. (Ed) Schlesinger, PhD
Benjamin T. Rome Dean
Whiting School of Engineering

Sangwon Kim, PhD
Associate Professor of Medicine
Retreat Committee Co-chair

Jamie Spangler, PhD
Assistant Professor of Biomedical Engineering, Chemical & Biomolecular Engineering
Retreat Committee Co-chair

KEYNOTE SPEAKER



Michael Snyder, PhD

Chair, Department of Genetics
Director, Center for Genomics and Personalized Medicine
Stanford University School of Medicine

Michael Synder is the Stanford Ascherman Professor and Chair of Genetics and the Director of the Center of Genomics and Personalized Medicine. Dr. Snyder received his PhD training at the California Institute of Technology and carried out postdoctoral training at Stanford University. As a pioneer of Precision Medicine, he has invented many technologies enabling the 21st century of healthcare including systems biology, RNA sequencing, and protein chip. Dr. Snyder has initiated the Big Data approach to healthcare through his work using omics to detect early stage disease, including wearables to detect infectious diseases like COVID-19, and at-home microsampling to measure hundreds of molecules from a single drop of blood. He is the first researcher to gather petabytes of data on individuals, which is 1 Million - 1 trillion times more data than the average clinician collects. He as published over 800 papers and is one of the most cited scientists. In terms of commercial success, he has co-founded 17 companies (including two unicorns) with combined enterprise value of over $6 billion.

MENTORING AWARD WINNERS

David M. Levine Excellence in Mentoring Award

William Checkley, MD, PhD

Professor of Medicine, Division of Pulmonary & Critical Care Medicine

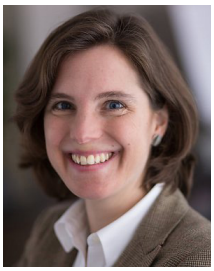
Dr. Checkley specializes in intensive care medicine. He is an expert in the diagnosis and management of acute respiratory failure and the acute respiratory distress syndrome. He also has extensive experience in the management of other life-threatening conditions commonly seen in the medical intensive care unit, including septic shock, acute gastrointestinal bleeding, acute liver failure, among other critical conditions. Dr. Checkley earned his M.D. from Northwestern University and received his Ph.D. from Johns Hopkins University. He completed his internal medicine residency training at Emory University and fellowship training in pulmonary and critical care medicine at Johns Hopkins School of Medicine. His research interests include International lung health, epidemiology, mechanical ventilation and acute lung injury.

Quote About Dr. Checkley:

"Dr. Checkley exemplifies all of the traits faculty at Johns Hopkins should strive to model, that is, an incredibly productive, groundbreaking and innovating physician-scientist while providing unselfish, personalized, thoughtful mentorship to junior faculty."

-Eric McCollum, MD

David M. Levine Excellence in Mentoring Award



Elizabeth Selvin, PhD, MPH

Co-Director, Cardiovascular Disease Epidemiology Training Program
Johns Hopkins Bloomberg School of Public Health
Joint Appointment in Medicine, Division of General Internal Medicine

Dr. Selvin holds a joint appointment in medicine at the Johns Hopkins University School of Medicine. She is a professor of epidemiology at the Johns Hopkins Bloomberg School of Public Health. Dr. Selvin's research focuses on diabetes and cardiovascular epidemiology. Her work on the association of hemoglobin A1c (HbA1c) with complications and its role in the diagnosis of diabetes has directly influenced clinical practice guidelines. Her team is currently engaged in the study of biomarkers and diagnostics relevant to diabetes and its complications. Dr. Selvin received her B.A. from Northwestern University. She earned her M.P.H. from the University of Michigan and her Ph.D. from the Johns Hopkins Bloomberg School of Public Health.

Quote About Dr. Selvin:

"Dr. Selvin…is constantly teaching, elevating and inspiring those around her, and has launched the careers of many of us to heights we never envisioned. We are very honored to write this letter in support of Dr. Selvin for the David M. Levine Excellence in Mentoring Award, and can think of no one more deserving of the recognition."

-Caitlin Hicks, MD & Lawrence Appel, MD, MPH

MENTORING AWARD WINNERS CONTINUED

Frederick L. Brancati Excellence in Mentoring Award

Luigi Adamo, MD, PhD

Director, Cardiac Immunology
Assistant Professor of Medicine, Division of Cardiology

Dr. Adamo is a physician-scientist and the director for Cardiac Immunology in the Johns Hopkins University Division of Cardiology. Born and raised in the south of Italy, after completing medical school, Dr. Adamo moved to the U.S. to pursue a Ph.D. in Biology and Biomedical Sciences at Harvard Medical School. He then went to Washington University School of Medicine where he completed post-graduate training in internal medicine, cardiovascular disease and advanced heart failure/cardiac transplant. He finally returned to basic science to complete post-doctoral training in cardiac immunology. Dr. Adamo is involved in both basic research and clinical research. His basic research focuses on the relationship between the immune system and the heart, in health and disease. His clinical research has focused on heart failure with normalized ejection fraction and patient selection for mechanical circulatory support.

Quote About Dr. Checkley:

"Our careers will forever be touched by the boundless energy, optimism and creativity which he embodies. I hope to bring the same attitude and gusto to my future mentorship relationships."
-Jana Lovell, MD

Department of Medicine & Whiting School of Engineering

2024 RESEARCH RETREAT

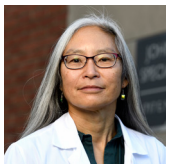
Spotlight on Research Talks

FRIDAY, FEBRUARY 9, 10:00-10:40 a.m. (Turner Auditorium)

The Spotlight on Research is a fast-paced session that showcases some of the past year's best science from the Johns Hopkins Department of Medicine and the Whiting School of Engineering. Each presenter will share higlights of their research findings delivered in a five-minute lighning talk.

Seda Aslan, MS
PhD student in Mechanical Engineering
"Virtual Planning and Patient-Specific Graft Design for Aortic Repairs"

David Gracias, PhD
Professor, Chemical and Biomolecular Engineering
"Autonomous Untethered Microinjectors for Gastrointestinal Delivery of Insulin"



Chloe Thio, MD
Professor of Medicine
Division of Infectious Diseases
"Integrated hepatitis B virus DNA maintains surface antigen production during antiviral treatment"

Felipe Andrade, MD PhD
Associate Professor of Medicine
Division of Rheumatology
"An unexpected origin of anti-DNA antibodies in SLE"

Kalina Hristova, PhD
Professor of Materials Science and Engineering
"Ligand and mutation-induced bias in EGFR signal transduction"

Kalen Clifton, BS
Doctoral Candidate in Department of Biomedical Engineering and Center for Computational Biology
"STalign: A Software Tool for Alignment of Spatial Transcriptomics Data"

Melanie Dispenza, MD, PhD, FAAAAI
Assistant Professor
Division of Allergy and Clinical Immunology
"Rapid prevention of food-induced anaphylaxis with oral kinase inhibitors"

Stephen Meltzer, MD
Professor of Medicine & Oncology
Division of Gastroenterology
"Genome Editing of Human Organoids Reveals Involvement of Key Lipids in Gej-Cardia Cancer Pathobiology"

Department of Medicine & Whiting School of Engineering

2024 RESEARCH RETREAT

Committee Members

Co-Chairs:

Sangwon Kim, PhD
Jamie Spangler, PhD

Members:

Peter Abadir, MD
Clifton Bingham, MD
Steven Clipman, PhD, MSPH
Christine Durand, MD
D. Brian Foster, PhD
Ankit Garg, MD, PhD
Claire Hur, MS, PhD
Deok-Ho Kim, PhD
Maximilian Konig, MD
Waseem Khaliq, MBBS, MPH
Gregory Lucas, MD, PhD
Laureano Moro Velazquez, PhD
Enid Neptune, MD
Brian O'Rourke, PhD
Jude Phillip, PhD
Faisal Rahman, BM, MBBCh, BCH
Matthew Robinson, MD
Prasanna Santhanam, MD
Florin Selaru, MD
Maunank Shah, MD
Larissa Shimoda, MS, PhD
Paul Welling, MD
William Werbel, MD, PhD

Event Coordinators:

Kelsey Bennett
Helen Harrison
Alissa Meehan
Melanie Mossman
Rebecca Spriggs

(Listed alphabetically)

Department of Medicine & Whiting School of Engineering

2024 RESEARCH RETREAT

Program

FRIDAY, FEBRUARY 9

8:30 a.m.

Welcome & Opening Remarks (Turner Auditorium)

Sangwon Kim, PhD
Associate Professor of Medicine
Retreat Committee Co-chair

Nadia N. Hansel, MD, MPH
Interim Director, Department of Medicine
Interim Physician-in-Chief, Johns Hopkins Hospital

T.E. "Ed" Schlesinger, PhD
Benjamin T. Rome Dean
Whiting School of Engineering

Jamie Spangler, PhD
Assistant Professor of Biomedical Engineering,
Chemical & Biomolecular Engineering
Retreat Committee Co-chair

Peter Abadir, MD
Associate Professor of Medicine
Geriatric Medicine & Gerontology
Retreat Committee Member

9:00 a.m.

Keynote Address (Turner Auditorium)

Michael P. Snyder, PhD
Chair, Department of Genetics
Director, Center for Genomics and Personalized Medicine
Stanford University School of Medicine

10:00 a.m.

Spotlight on Research Talks (Turner Auditorium)
Moderated by Peter Abadir, MD and Jamie Spangler, PhD

Seda Aslan, MS
PhD Student, Mechanical Engineering

Chloe Thio, MD
Professor of Medicine, Infectious Diseases

Kalina Hristova, PhD
Professor, Materials Science and Engineering

Melanie Dispenza, MD, PhD, FAAAAI
Assistant Professor of Medicine
Allergy and Clinical Immunology

David Gracias, PhD
Professor, Chemical and Biomolecular Engineering

Felipe Andrade, MD, PhD
Associate Professor of Medicine, Rheumatology

Kalen Clifton, BS
Doctoral Candidate, Biomedical Engineering

Stephen Meltzer, MD
Professor of Medicine & Oncology, Gastroenterology

10:40 a.m.

Mentoring Awards (Turner Auditorium)
Presented by Jeanne Clark, MD

The David M. Levine Excellence in Mentoring Awards
The Frederick L. Brancati Excellence in Mentoring Award

10:50 a.m.

Break

11:00 a.m.

Research Award Presentations (Turner Auditorium)

The W. Leigh Thompson Excellence in Research Awards
Presented by Brian O'Rourke, PhD and Clifton Bingham, MD

Basic Fellow Winner - Akshay Sanghi, MD, PhD
Basic Faculty Winner - Xiangbo Ruan PhD
Clinical Fellow Winner - Richard Carrick MD, PhD
Clinical Faculty Winner - Lolita Nidadavolu MD, PhD

Whiting School of Engineering Research Awards
Presented by Jamie Spangler, PhD

Trainee Winners - Sue Min Cho, MSE, PhD
Michael Waight, MD
Faculty Winner - Kimia Ghobadi, MSc, MEng, PhD

11:45 a.m.

Lunch Break (Turner Consourse)

12:15 p.m.

Poster Session: Odd Numbers (Turner Consourse)

1:15 p.m.

Poster Session: Even Numbers (Turner Consourse)

2:15 p.m.

Retreat Closing

THE W. LEIGH THOMPSON EXCELLENCE IN RESEARCH AWARD

Basic Research Fellow Winner

Akshay Sanghi, MD, PhD Abstract 58

"Integrating epigenetic regulation with metabolic signaling in aggressive thyroid cancer"

Finalists

Mohammad Keykhaei Abstract 1

Nour Naji Abstract 28

Shannon Niedermeyer Abstract 72

Paula Reventun Abstract 97

Basic Research Faculty Winner

Xiangbo Ruan, PhD Abstract 12

"A novel non-coding genetic variant affects blood lipids by regulating a human-specific long non-coding RNA"

Finalists

Elizabeth Luczak Abstract 118

Reyhan Westbrook Abstract 83

THE W. LEIGH THOMPSON EXCELLENCE IN RESEARCH AWARD

Clinical Research Fellow Winner

Richard Carrick, MD, PhD Abstract 11

"Identification of High-Risk Imaging Features in Hypertrophic Cardiomyopathy Using Electrocardiography: A Deep-Learning Approach"

Finalists

Ashkan Abdollahi Abstract 114

Aida Metri Abstract 66

Matthew Meyers Abstract 87

Chigolum Oyeka Abstract 64

Clinical Research Faculty Winner

Lolita Nidadavolu, MD, PhD Abstract 79

"Identifying frailty sub-populations based on cell-free DNA tissue of origin "

Finalists

Ravi Gupta Abstract

Joban Vaishnav Abstract 36

WHITING SCHOOL OF ENGINEERING RESEARCH AWARD

Trainee Awardees

Sue Min Cho, MSE, PhD Abstract 163

"Human-centered assurance in technology-assisted surgery"

Michael Waight, MD Abstract 5

"Determining the Accuracy of MRI-based Computational Modelling in Predicting Critical Substrate in Ventricular Tachycardia"

Lab Excellence Award

Kimia Ghobadi, MSc, MEng, PhD Abstract 164

"A prediction and optimization framework for improving hospital capacity management during demand surges"

Finalists

Fardin Ganjkhanloo Abstract 130

Derosh George Abstract 125

Francis Manno Abstract 140

Joshua Popp Abstract 65

Piyush Raj Abstract 31

Kehan Ren Abstract 22

Yutong Zhu Abstract 120

ABSTRACTS

ABSTRACT 1

Unraveling the Serine Synthesis Pathway: Implications for Altered Cardiac Metabolism in Heart Failure

Mohammad Keykhaei, Navid Koleini, Mariam Meddeb, Nathaniel Snyder, Farnaz Farshidfar, Virginia Hahn, Kavita Sharma, David Kass

Intro: Nearly 70 million people worldwide have heart failure (HF). Alterations in cardiac energy metabolism contribute to HF as the failing heart exhibits metabolic inflexibility, although little human data exists. Our transcriptomic and metabolomic data revealed striking metabolic defects not predicted by animal models. We have extended these in new data identifying a particularly profound decline in proximal glycolysis intermediates and the denovo serine synthesis (SSP).

Hypothesis: Here, we hypothesis that insufficient SSP inhibits purine synthesis and one-carbon metabolism, increasing oxidant imbalance and resulting in mitochondrial dysfunction, contributing to a HF phenotype.

Methods and Results: We discovered that myocardial serine levels decreased in human HF. Serine derives from exogenous sources or a de novo SSP. The latter requires phosphoglycerate dehydrogenase (PHGDH) the rate-limiting step. In new data, we show PHGDH and other key enzymes in SSP are reduced in HF. Importantly, gene knockdown (KD) of PHGDH markedly lowers adult cardiomyocytes serine despite exogenous sources, and induces marked cytotoxicity within 24 hours far more than from depleting serine in the media. This suggests de novo SSP is key for cellular homeostasis in cardiomyocytes. PHGDH inhibition also markedly lowers basal and endothelin-1 (ET1) stimulated mitochondrial respiration coupled to impaired glutathione antioxidant balance, and mitochondrial DNA copy number.

Conclusion: Our study identifies SSP as a pivotal metabolic pathway in the development of HF. Investigating metabolic defects to enhance HF treatment is a key research goal, and the focus on serine opens a novel and potentially significant therapeutic avenue.

ABSTRACT 2

TSC2-mTOR Axis Exerts Biased Control over Macrophage Infiltration Following Myocardial Infarction

Mohammad Keykhaei, Navid Koleini, Mariam Meddeb, Mark J Ranek, David Kass

Introduction: The mechanistic target of rapamycin complex 1 (mTORC1) is an evolutionarily conserved serine/threonine kinase, which regulates pivotal physiological processes. mTORC1 activity is tightly regulated upstream by the tuberous sclerosis complex (TSC). In macrophages, mTORC1 is a potent regulator of cell activation. Myocardial infarction (MI) is associated with stimulation of mTORC1; however, studies vary as to whether this activation is beneficial or detrimental.

Hypothesis: We tested the hypothesis that cardiac infiltration of macrophages following MI is regulated by their expression of TSC2.

Methods/Results: We generated macrophage-specific-TSC2 knock-out-mice (TSC2-LyzM). TSC2-LyzM bone-marrow-derived-macrophages (BMDMs) have constitutive mTORC1 activation reflected by phosphorylation of downstream targets S6K1 and 4E-BP1 and were correspondingly larger. To assess macrophage polarization, cells were stimulated with LPS to promote an M1-like phenotype or IL-4 to induce an M2-like phenotype. LPS- treated TSC2-LyzM BMDMs secreted more of the proinflammatory cytokine, while IL-4 stimulation resulted in less of an M2 program. These findings show TSC2 is required for normal BMDM polarization. We next tested if TSC2 impacts macrophage myocardial infiltration after MI. Macrophages were identified as CD45+CD11b+CD64+ and further parsed by CCR2 and MHC-II. We found substantial infiltration of CCR2+ (BMDMs) macrophages in both genotype groups after MI. However, more TSC2-LyzM had increased CCR2+ MHC-II+ phenotype versus wild-type. Besides, TSC2-LyzM mice showed better cardiac function after I/R.

Conclusion: Overall, our findings highlight a key role for the TSC2-mTORC1 pathway in regulating macrophage fate specification and cardiac infiltration following MI.

ABSTRACT 3

Integrated Multiomics Landscape of Cardiac Metabolism in Human Heart Failure with Preserved Ejection Fraction

Mohammad Keykhaei, Vivek P Jani, Edwin Yoo, Virginia Hahn, Navid Koleini, Kavita Sharma, David A Kass

Introduction: There are 6-7 million adults with heart failure (HF) living in the United States, half of whom have HF with preserved ejection fraction (HFpEF). Here, we report the first integrated analysis of myocardial metabolomics, transcriptomics, and proteomics identifying defective metabolic pathways in HFpEF.

Results: Glycolytic proteins were not significantly altered in HFpEF, but protein and gene expression of GLUT1 was lower in HFpEF over the controls. Pyruvate and acetyl-coA metabolites and protein expression of pyruvate kinase M were higher in HFpEF, while pyruvate dehydrogenase kinase 4 expression was lower, suggesting an increase toward pyruvate oxidation. The tricarboxylic acid (TCA) cycle displayed broad reductions in key proteins in HFpEF, with lower aconitase, succinate-CoA ligase GDP-Forming Subunit Beta, succinate dehydrogenase, citrate, fumarate, and succinate. Fatty acid uptake, lipolysis, oxidation, and master regulators of FA oxidation were all lower in HFpEF. This was striking, given the massive obesity in most of the patients. Consistent with these changes, medium and long-chain acylcarnitines were broadly lower in HFpEF myocardium. Ketone metabolism rises in HFrEF as an alternative fuel, but in HFpEF, we found ketogenesis-related genes lower overall vs. Controls, and C4-OH beta-hydroxybutyryl, a downstream metabolite of ketone bodies, was lower in HFpEF. Lastly, branched-chain amino acids were higher in HFpEF over control, whereas the primary catabolites and gene and protein expression of enzymes involved were lower in HFpEF vs. Control.

Conclusion: Our results suggest striking fuel inflexibility of the HFpEF myocardium, involving defects in glucose utilization, TCA cycle, FA oxidation, ketogenesis, and BCAA metabolism.

ABSTRACT 4

Neural operators to detect aortic aneurysm contributors

Somdatta Goswami, David Li, Jay D. Humphrey, and George Em Karniadakis

A thoracic aortic aneurysm (TAA) is a localized dilatation of the aorta that can lead to life-threatening dissection or rupture. In vivo assessments of TAA progression are largely limited to measurements of aneurysm size and growth rate. There is a promise, however, that computational modeling of the evolving biomechanics of the aorta could predict future geometry and properties from initiating mechanobiological insults. We present an integrated framework to train a deep operator network (DeepONet)--based surrogate model to identify TAA contributing factors using synthetic finite-element-based datasets. For training, we employ a constrained mixture model of aortic growth and remodeling to generate maps of local aortic dilatation and distensibility for multiple TAA risk factors. The performance of the surrogate model is evaluated for insult distributions varying from fusiform (analytically defined) to complex (randomly generated). We propose two frameworks, one trained on sparse information and one on full-field greyscale images, to gain insight into a preferred neural operator-based approach. We show that this continuous learning approach can predict the patient-specific insult profile associated with any given dilatation and distensibility map with high accuracy, particularly when based on full-field images.

ABSTRACT 5

Determining the Accuracy of MRI-based Computational Modelling in Predicting Critical Substrate in Ventricular Tachycardia

Michael Waight, Adityo Prakosa, Anthony Li, Magdi Saba, Natalia Trayanova

MRI-based virtual heart modelling can be used to demonstrate inducibility of arrhythmia and predict optimum ablation lesion sets for patients with ventricular tachycardia (VT). The accuracy of virtual heart modelling to predict critical substrate abnormalities in VT remains unknown.

18 patients with scar-dependent VT underwent cardiac MRI followed by virtual heart modelling. Simulated ventricular pacing was performed to demonstrate VT inducibility and predict optimum lesion sets that terminate all likely VTs in the models. Predicted lesion sets were merged with the electroanatomical map obtained during VT ablation. Electrogram (EGM) abnormalities and duration were compared between predicted and non-predicted sites within bipolar low voltage (<1.5mV) regions. During VT, predicted site locations were correlated with mid-diastolic potentials (MDPs) - a surrogate for the VT isthmus.

7699 bipolar EGMs were analysed. There was no difference in voltage between predicted and non-predicted sites (0.31mV vs 0.32, $p = 0.62$). EGM abnormalities were more frequent in predicted EGMs (468/1029 [45.5%]) compared to non-predicted EGMs (519/1611 [32.2%]). $p < 0.001$. EGM duration was longer at predicted sites compared to non-predicted sites (82.0ms vs 69.7ms, $p < 0.001$).
MDPs were recorded in 16/43 (37.2%) of induced VTs. 13/16 (81.3%) of MDPs were located within 5mm of a predicted area vs 3/16 (18.8%) which were remote ($p < 0.001$).

Virtual heart predicted targets display a greater prevalence of EGM abnormalities, longer EGM duration and are more frequently co-located with markers of the VT isthmus than non-predicted, voltage-matched areas. Computational modelling may improve the accuracy of VT ablation.

ABSTRACT 6

Intranasal delivery of a novel DNA therapeutic vaccine targeting the Mycobacterium tuberculosis stringent response factor RelMtb to dendritic cells shortens the duration of curative TB treatment

Karanika Styliani, Yilma Addis, Wang Tianyin, Ruelas Castillo Jennie, Quijada Darla, Bailey Hannah, Gordy James, Chen Iris, Karantanos Theodoros, Markham Richard, Karakousis Petros

BACKGROUND: Host status plays a major role in tuberculosis (TB) disease outcomes, with efforts underway to develop host-directed therapies. The stringent response protein RelMtb plays an important role in Mtb persistence, contributing to the prolonged treatment required to eradicate infection. We developed a novel therapeutic DNA vaccine after fusing the relMtb gene with the gene encoding the immature dendritic cell-targeting chemokine, MIP-3α. We sought to determine if intranasal administration of this novel fusion vaccine shortens the duration of curative TB treatment.

DESIGN/METHODS: We compared the efficacy of this intranasal fusion DNA vaccine combined with the standard daily four-drug regimen [Rifampin (R), Isoniazid (H), Pyrazinamide (Z), Ethambutol (E)] vs. RHZE alone in a murine model of chronic TB. The intranasal vaccine was administered in 3 doses, at one-week intervals, with daily RHZE by oral gavage. Twelve weeks following prime vaccination, treatment was discontinued to assess for microbiological relapse. Final harvesting was performed to evaluate the antimycobacterial efficacy at 24 weeks post-prime vaccination.

RESULTS: The group receiving the intranasal MIP-3α/relMtb DNA vaccine combined with RHZE achieved culture negativity after 12 weeks of treatment in contrast to RHZE alone ($P<0.0001$). The intranasal MIP-3α/relMtb DNA vaccination group produced stable cure, as shown after 12-week treatment discontinuation.

CONCLUSION: Intranasal therapeutic immunization with a DNA vaccine expressing MIP-3α/RelMtb is a novel adjunctive host-directed therapy for shortening the duration of the standard regimen for drug-susceptible TB. This novel strategy functions independently of antibiotic resistance status, and it may be extended as a therapeutic strategy for multidrug-resistant TB.

ABSTRACT 7

ddPCR detects HBV DNA and RNA in the majority of livers after HBsAg loss

Tanner Grudda, David L. Thomas, Gregory D. Kirk, Shruti H. Mehta, Jacquie Astemborski, Georg M. Lauer, Ashwin Balagopal, Chloe L. Thio

After HBsAg loss, viral DNA or RNA in the liver has not been carefully documented though is assumed present since HBV can reactivate during immunosuppression. To quantify the burden of HBV in the liver following recovery, we compared seven liver resections (range:6.1-6.3log10 hepatocytes) without past or current HBV infection or injection drug use (Controls) to 13 liver biopsies (range:4.5-6.4log10 hepatocytes) from people with HBV Recovery (HBcAb(+)/HBV DNA(-)/HBsAg(-)) and chronic hepatitis C followed longitudinally in the AIDS Linked to the IntraVenous Experience Study (ALIVE). Fourteen liver tissue slide scrapes (range:2.3-5.4log10 hepatocytes) from people with HBV Recovery in ALIVE were also examined. Recovery occurred primarily without treatment [slide scrapes:11/14; whole biopsies:12/13]. Cells/biopsy or slide scrape were quantified by ERV3 qPCR and RNA integrity was confirmed by measuring hepatocyte housekeeping genes. Quantifying six targets by ddPCR–total HBV DNA, cccDNA, four RNA transcripts tiled across the genome–we performed 42 independent measurements in Control whole biopsies and 78 in Recovery whole biopsies detecting HBV targets in 1 and 18 measurements, respectively ($p<0.01$). The 18 positive targets were identified in 8/13 Recovery biopsies (DNA in 6 and RNA in 7 whole biopsies). Extrapolating from total HBV DNA/cell of whole biopsies to the entire liver, the median burden of total HBV DNA among positive biopsies was 7.0log10 copies (range:5.5-7.8log10). Likewise, the median burden of HBV RNA in the entire liver, calculated using the most frequently detected amplicon, was 6.3log10 copies (range:5.6-7.1log10). Recovery slide scrapes, with an average 5.9log10 fewer hepatocytes than whole biopsies, had only 1/84 measurements with HBV targets supporting that measuring greater numbers of hepatocytes increases the ability to detect HBV in livers following HBsAg loss. In summary, we underscore the difficulties in achieving complete HBV eradication since the majority of livers have detectable, transcriptionally active HBV DNA after HBsAg loss.

ABSTRACT 8

Enhancing Ear ECG Analysis during CPR Using Adaptive Filtering

Prachi Agarwal, Yu Guo, Nitish V. Thakor

This study explores the feasibility of using ear electrocardiogram (ECG) as a viable alternative to the traditional chest ECG during cardiopulmonary resuscitation (CPR). To ensure the reliability of the ear ECG in identifying the QRS complex within the cardiac cycle, the Bald-Altman plot is used for validation. Adaptive filters are employed to suppress artifacts caused by chest compressions (CCs) and restore clinically significant ECG information. The performance evaluation involves comparing artifact-free ECGs with filtered ECGs, considering the denoised signal-to-noise ratio (SNRden), Pearson's Correlation coefficient, and the Modified Bray-Curtis index. The extended-kernel recursive least squares filter proves to be the most effective option for both ear and chest locations. Notably, the ear ECG exhibits a higher mean SNRden (5.35 dB) compared to the gold-standard chest ECG (SNRden 2.83 dB). Our results suggest that the proposed technique could be a highly translational method for ECG measurements during CPR, which allows for uninterrupted CCs, eliminating the need to pause for rhythm analysis and potentially improving the efficiency and effectiveness of CPR procedures.

ABSTRACT 9

Diagnosis of Schizophrenia using a Novel Resting-State fMRI Marker of Regional Interactions in the Brain Network

Autumn Williams, Luis Sanchez, Sri Sarma

Schizophrenia is a complex mental disorder characterized by abnormal neural connectivity patterns. The gold standard for diagnosis requires structured interviews and visual examination of MRI by medical professionals. The high level of training and experience required for accurate diagnosis limits access to care from many patients. We investigated a potential quantitative method of diagnosing schizophrenia using resting-state fMRI.

We constructed dynamic network models to examine a novel biomarker, the "sink index," which characterizes how cortical region of interest (cROI) in the brain is influenced by its fellows. Under this paradigm, sources are regions that exert a significant influence but are not themselves influenced, while sinks represent regions heavily influenced that do not exert influence on others. We hypothesized that cROI associated with schizophrenia would present a different distribution of sink indices compared to healthy brains. Subjects included in this analysis were taken from an open dataset and divided into two cohorts of 34 healthy controls (ages 36±7.9, M 20) and 36 schizophrenia (ages 36.2±7.01, M 26, PANNS avg 60.2±17.3). We examined seventy (70) cROI. The distributions of the Sink Indices were then compared.

Our findings revealed significant differences in influence within six specific cROI between healthy controls and schizophrenia patients ($p<0.01$); all of the identified regions are known to play crucial roles in both positive and negative symptoms present in patients with schizophrenia. Using these regions we developed an elastic net regression-based classifier that was able to identify cohort membership with high accuracy (10fCV, sens 0.92, spec 0.82, AUC 0.9355). Our results provide further evidence supporting the hypothesis that aberrant network connectivity patterns contribute to the pathophysiology of this psychiatric disorder. The application of such models to large-scale rsfMRI datasets offers a promising avenue for identifying biomarkers for schizophrenia and other related disorders.

ABSTRACT 10

Multiscale mechanobiology shapes tissues in development

Shinuo Weng

Tissue morphogenesis is the process by which cells and tissues acquire their shape and function during embryonic development. While the design of a tissue is encoded in the genome, the execution of this program is driven by the mechanical progression of coordinated behaviors at molecular, cellular, and tissue scales. Therefore, understanding the emergence of biomechanical features and their functions in tissue morphogenesis across multiple scales is fundamental to understanding normal development and the etiology behind congenital malformations.

The Tissue Morpho & Mechanical Lab (TMML) emerges from my postdoc work on convergent extension (CE), a conserved collective cell movement essential for the elongation of the body axis and the formation of several organ systems such as neural tube, heart, and kidney. Through a multidisciplinary approach integrating embryology, mechanics, and computational modeling, our research reveals emergent mechanical features across multiple length and time scales crucial for CE.

Looking ahead, TMML directs its focus toward deciphering the intracellular and extracellular mechanical cues that coordinate cell movement for efficient and robust CE across various tissues. Our exploration will also extend to engineering applications aimed at recreating these mechanical blueprints, offering new approaches to guide tissue shaping in vitro. Please do not hesitate to reach out if you want to join us or start a collaboration.

ABSTRACT 11

Identification of High-Risk Imaging Features in Hypertrophic Cardiomyopathy Using Electrocardiography: A Deep-Learning Approach

Richard T. Carrick, Hisham Ahamed, Eric Sung, Martin S. Maron, Christopher Madias, Vennela Avula, Rachael Studley, Chen Bao, Nadia Bokhari, Erick Quintana, Rajesh Kannan, Barry J. Maron, Ethan J. Rowin, Katherine C. Wu

Background: Patients with hypertrophic cardiomyopathy (HCM) are at risk for sudden death, individuals with ≥1 major risk markers are considered for primary prevention implantable cardioverter defibrillators. Guidelines recommend cardiac magnetic resonance imaging (CMR) to identify high-risk imaging features. However, CMR is resource intensive and not widely accessible worldwide.

Objective: To develop electrocardiogram (ECG) deep-learning (DL) models for identification of HCM patients with high-risk features. Methods: HCM patients evaluated at Tufts Medical Center (Boston, United States (US); N=1,930) were used to develop ECG-DL models for prediction of high-risk imaging features: systolic dysfunction, massive hypertrophy (≥30mm), apical aneurysm, and extensive late-gadolinium enhancement (LGE). ECG-DL models were externally validated in an HCM cohort from Amrita Hospital (Kochi, India; n=233).

Results: ECG-DL models reliably identified high-risk features (systolic dysfunction, massive hypertrophy, apical aneurysm, and extensive LGE) during hold-out model testing (c-statistics 0.72, 0.83, 0.93, and 0.76) and external validation (c-statistics 0.71, 0.76, 0.91, and 0.68). A hypothetical screening strategy employing echocardiography combined with ECG-DL guided selective CMR use demonstrated sensitivity of 97% for identifying patients with high-risk features, while reducing the number of recommended CMR by 61%. Negative predictive value with this screening strategy for absence of high-risk features in patients without ECG-DL recommendation for CMR was 99.5%.

Conclusion: In HCM, novel ECG-DL models reliably identified patients with high-risk imaging features who benefit from CMR, thus offering potential to reduce CMR testing requirements in under-resourced areas.

ABSTRACT 12

A novel non-coding genetic variant affects blood lipids by regulating a human-specific long non-coding RNA

Xiangbo Ruan

Most disease-associated genetic variants in humans are poorly conserved among animal models, making it challenging to study their mechanisms of action at the tissue/organ level. In this study, we overcome this limitation by showing a blood lipid-associated genetic variant (rs9653945) functions by regulating a human-specific long non-coding RNA (LOC100507389). We first analyzed published human genetic data and found that rs9653945 is associated with blood cholesterol and triglyceride levels and the expression of LOC100507389 in human liver tissues. By performing CRISPR base editing in cultured human hepatocytes, we revealed that rs9653945 risk allele (G) is essential for glucose-induced expression of LOC100507389. To test the role of this rs9653945 (G)-LOC100507389 pathway in vivo, we prepared a humanized liver mouse model where mouse hepatocytes were replaced by human hepatocytes that are homozygous for rs9653945-G. We found that the expression of LOC100507389 is induced by feeding, and knocking down of LOC100507389 in humanized liver mice resulted in a broad downregulation of human genes in the glycolysis, lipogenesis, and cholesterol synthesis pathway. Furthermore, cholesterol levels in human Apolipoprotein B-containing lipoproteins were significantly lower upon knocking down LOC100507389. Finally, we found that hLMR1 and its downstream genes involved in lipid synthesis were significantly upregulated in the liver tissue of patients with coronary artery disease. In summary, using in vitro CRISPR base editing and in vivo functional analysis in humanized liver mice, our work supports a novel rs9653945 (G)-LOC100507389-hepatic lipid synthesis pathway that can be potentially targeted to treat hyperlipidemia-associated diseases.

ABSTRACT 13

Designing Patient-Specific Neurostimulation to Suppress Seizures

Emily A. Reed, Kyra Bowden, Arianna Damiani, Rachel June Smith, Jorge A. González-Martínez, Joon Y. Kang, and Sridevi V. Sarma

Approximately, 15 million people world-wide suffer from medically refractory epilepsy. Treatment of their uncontrolled seizures usually involves ablative or resective surgery, but with surgery success rates varying between 30-70%, physicians have turned to neurostimulation to treat this population of patients. However, one major difficulty in using these devices is to select the appropriate stimulation parameters, which is done via trial and error and can take months or even years to tune effectively. A patient-specific method that can identify effective stimulation parameters computationally is needed to deliver stimulation that suppresses seizures.

Suppressing seizures is not only important for enhancing the quality of life of patients with epilepsy, but it may also save lives. In this work, we present a data-driven patient-specific method that identifies an effective stimulation frequency to suppress seizures by leveraging the patient's cortico-cortical evoked potentials (CCEPs). Using CCEPs data, we construct a dynamical network model and examine its frequency response from which we select the frequency that minimizes the response, known as the "zero" frequency.

We retrospectively demonstrate the effectiveness of stimulating at the "zero" frequency on five medically refractory epileptic patients. We show that the norm of the signals in the seizure onset zone is smaller when stimulated at the "zero" frequency as compared with the norm of these signals when stimulated at various other frequencies. This work lays the foundation for designing data-driven patient-specific neurostimulation to be an effective treatment for medically refractory epilepsy. Future work will focus on prospectively validating this method in the clinic.

ABSTRACT 14

Blood pressure Trends in Heart Failure With Preserved Ejection Fraction

Che-Min Lo, Wentao Zhan, Ruzhang Zhao, Hongkai Ji, Chloe L. Thio, Ashwin Balagopal

Scant data exist about intrahepatic cellular responses during chronic hepatitis B (CHB). We hypothesized that host factors modulate the heterogeneity in HBV cccDNA transcription during nucleos(t)ide analogue therapy.

We analyzed the transcriptome of fresh-frozen liver biopsies from eight HBV-HIV co-infected individuals with hepatitis B e antigen positive CHB under varying exposure to antiviral treatment. We used Seurat in R to integrate tissues and cluster spots by transcriptional profiles.

We analyzed 17,602 genes across 9,825 cell spots, identifying three key cell populations: hepatocytes (n=8,565 spots), lymphocytes (n=1,164 spots), and dendritic cells (n=101 spots). Hepatocytes were stratified into high (n=1,330) (median normalized HBV expression; IQRs: 1.93; 1.77-2.16) and low (n=1,330) (0.38; 0.1-0.5) HBV-transcribing groups. Differential gene expression analysis (DGEA) was performed on hepatocyte clusters. We demonstrated 441 upregulated and 11 downregulated host genes in spots with active HBV expression (log2 fold-change > 1.7, adjusted p-value < 0.05). Over-representation analysis (ORA) indicated enrichment in liver function pathways for high HBV expression (e.g., upregulated genes: plasminogen activation, adjusted p-value=9.32e-09; downregulated genes: acyl-CoA metabolism, adjusted p-value=4.89e-03).

Using spatial transcriptomics, we found that HBV transcription was closely associated with host metabolic processes and immune responses. These findings underscore the intricate dynamic between HBV and host cellular machinery, potentially offering insights into genes affecting HBV transcription.

ABSTRACT 15

The source of hepatitis B surface antigen (HBsAg) in individual hepatocytes shifts from cccDNA-derived to integrated HBV DNA (iDNA)-derived with nucleos(t)ide analogue (NUC) therapy

Maraake Taddese, Tanner Grudda, Hyon S. Hwang, Yasmeen Saad, Kristina Zambo, Naomi Esrig, Mark S. Sulkowski, Richard K. Sterling, Ashwin Balagopal, Chloe L. Thio

HBsAg derives from either cccDNA or integrated HBV DNA (iDNA). We examined the dynamics of cccDNA- or iDNA-derived HBsAg production in infected hepatocytes during nucleos(t)ide analogue (NUC) treatment.

We investigated paired liver biopsies from 10 people with HBV and HIV, stratified by NUC duration at biopsy 1: early group—five (4 HBeAg+, 1 HBeAg-seroconverter between biopsies) recently started NUCs (median 0.6 years); prolonged group—five (1 HBeAg+, 4 HBeAg-) on long-term NUCs (median 7 years, HBV DNA undetectable). From individual hepatocytes (median 172/biopsy), we used ddPCR to discriminate between cccDNA- and iDNA-derived transcripts using the ratio of the quantities from two amplicons: mid-HBV capturing 3.5kb, 2.4kb, and 2.1kb transcripts to 3'-HBV capturing cccDNA-derived transcripts.

Proportions of cells without viral transcripts were lower in the early than prolonged group at biopsy 1 (median 0.8% vs 83.5%, p<.00001) and biopsy 2 (median 20.8% vs 89.7%, p=.0002). Proportions of iDNA-only transcribing cells at biopsy 1 were lower in the early than prolonged group (median 3% vs. 48%, p=.002), but enriched with NUCs to 12% at biopsy 2. In the early group, serum qHBsAg declined >0.5 log10IU/ml between biopsies in all but one individual in whom there was a transcriptional shift in individual hepatocytes from 88% cccDNA-only to 92% iDNA-only. In the prolonged group, a greater number of viral transcripts were derived from iDNA; correspondingly, qHBsAg was stable between biopsies. However, in each biopsy in the prolonged group, a proportion of cells producing viral transcripts had chiefly cccDNA-derived transcription. Notably, the observations in the prolonged group were similar for the one HBeAg+ individual and the HBeAg- contemporaries.

During NUCs, HBV transcription decreases globally, the proportion of cells with iDNA-derived transcription enriches while subpopulations of cells maintain cccDNA-derived transcription. Thus, therapies adjunctive to NUCs need to address iDNA-derived and residual cccDNA-derived transcription to achieve functional cure.

ABSTRACT 16

Revisiting registration-based synthesis: a focus on unsupervised MR image synthesis

Savannah P. Hays, Lianrui Zuo, Yihao Liu, Jiachen Zhuo, Jerry L. Prince, and Aaron Carass

Background: Although diagnosed and treated for psychotic disorders, relapse occurs commonly after appropriate treatment. Digital phenotyping, moment-by-moment quantification of individual-level data collected from personal mobile devices, becomes essential to achieve remote monitoring of symptoms and treatment responses for psychotic patients, especially relapse.

Methods: We propose a novel application of predicting relapse for patients in the psychotic spectrum using unsupervised, neural-net-based anomaly detection and clustering to identify abnormal behavioral changes. We use a dataset provided by e-Prevention and ICASSP Signal Processing Grand Challenge (SPGC) 2023, which contains physiological signals (e.g., movement, cardiac activity, sleep) for 10 patients over 6-month period. We consider consecutive minute information as a form of 2D images, learned latent features via a convolutional autoencoder (CAE), and identified clusters regarding relapse status on personalized schemes (i.e., training separate models based on each individual patient).

Results: Our model achieves promising and comparable results with the 1st SPGC on the leaderboard (CAE + clustering: ROC-AUC = 0.607, PR-AUC = 0.698, harmonic mean = 0.649; 1st place of SPGC: ROC-AUC = 0.647, PR-AUC = 0.651, harmonic mean = 0.649). Our results also add to existing evidence of detecting relapse more easily using data collected during sleeping period.

Discussion: Our preliminary study demonstrates the power of unsupervised learning in identifying abnormal behavioral changes in psychotic patients, which could be applied to treating other mental disorders and improving their quality of life with timely intervention and lower cost of care.

ABSTRACT 17

Relapse prediction through convolutional autoencoders and clustering for psychotic patients using wearable data

April Yujie Yan

Background: Although diagnosed and treated for psychotic disorders, relapse occurs commonly after appropriate treatment. Digital phenotyping, moment-by-moment quantification of individual-level data collected from personal mobile devices, becomes essential to achieve remote monitoring of symptoms and treatment responses for psychotic patients, especially relapse.

Methods: We propose a novel application of predicting relapse for patients in the psychotic spectrum using unsupervised, neural-net-based anomaly detection and clustering to identify abnormal behavioral changes. We use a dataset provided by e-Prevention and ICASSP Signal Processing Grand Challenge (SPGC) 2023, which contains physiological signals (e.g., movement, cardiac activity, sleep) for 10 patients over 6-month period. We consider consecutive minute information as a form of 2D images, learned latent features via a convolutional autoencoder (CAE), and identified clusters regarding relapse status on personalized schemes (i.e., training separate models based on each individual patient).

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Discussion: Our preliminary study demonstrates the power of unsupervised learning in identifying abnormal behavioral changes in psychotic patients, which could be applied to treating other mental disorders and improving their quality of life with timely intervention and lower cost of care.

ABSTRACT 18

A high-dimensional multiplex ddPCR assay to quantify the diversity and frequency of hepatitis B virus splice variant RNAs

Chenkai Jiang, Tanner Grudda, Ashwin Balagopal, Chloe L. Thio

Hepatitis B virus (HBV) chronically infects 316 million people. This study addresses the challenge of detecting and quantifying HBV splice variants (spHBVs) in infected individuals, a critical step in understanding HBV persistence and aiding in the development of targeted therapies. We introduce a highly sensitive and specific multiplex droplet digital PCR (ddPCR) assay for the absolute quantification of four prominent HBV splice variants (sp1, sp2, sp3, and sp9). The assay, optimized through extensive primer and probe design, temperature controls, and amplification procedures, demonstrates remarkable precision and efficiency. Notably, it overcomes the limitations of traditional quantitative PCR and next-generation sequencing by offering a cost-effective and less labor-intensive alternative, capable of direct application to serum, liver, and cell-extracted splice variants. Our findings not only provide a reliable method for spHBV detection but also contribute to the broader understanding of HBV biology and the development of HBV cure strategies. This work paves the way for future investigations into the transcriptional mechanisms of covalently closed circular DNA and the role of spHBVs in HBV pathogenesis and resistance to therapy.

ABSTRACT 19

Unveiling Parkinson's Disease: Probing the Prodromal Phase with Longitudinal Speech Analysis for Early Detection and Monitoring

Anna Favaro, Ankur Butala, Thomas Thebaud, Jesús Villalba, Najim Dehak, Laureano Moro-Velázquez

In the last decade, numerous studies have proposed models for detecting and continuously monitoring Parkinson's disease (PD) through speech analysis. However, existing speech data sets for these purposes suffer from limitations such as lack of recordings in the prodromal period, limited sample size, and absence of longitudinal data. To address these drawbacks, this study introduces ParkCeleb, a longitudinal data set tailored to monitor and detect PD from speech. Via an almost fully automated pipeline, we collected online videos featuring 86 celebrities, 43 diagnosed with PD, and 43 control subjects. We conducted a longitudinal study on this data set to monitor the temporal evolution of various speech features, starting up to 10 years before diagnosis (prodromal phase) and considering an average observation period of 20 years. We also created machine-learning binary classifiers (PD vs controls) and performed mono-, multi-, and cross-corpora experiments employing other already existing data sets. The longitudinal analysis revealed distinctive features such as pause duration, speech rate, and syllable duration, displaying temporal evolutions specifically associated with the progression of PD. Across various classification experiments, a notable finding emerged: early patterns of dysarthria are detectable in the prodromal phase of the disease 10 years before diagnosis in some subjects. Importantly, these patterns can be leveraged in the development of early detection techniques, even when utilizing post-diagnosis speech recordings from other cohorts to train the models. In essence, this study sheds light on the possibility of developing early detection methods that can potentially serve to identify early treatment responses and that can serve as screening tools in clinical trials.

ABSTRACT 20

Pushing the limits of zero-shot self-supervised super-resolution of anisotropic MR images

Samuel W. Remedios, Shuwen Wei, Blake E. Dewey, Aaron Carass, Dzung L. Pham, Jerry L. Prince

Magnetic resonance images are often acquired as several 2D slices and stacked into a 3D volume, yielding a lower through-plane resolution than in-plane. Many super-resolution (SR) methods have been proposed to address this, including those that use the inherent high-resolution (HR) in-plane signal as HR data to train deep neural networks. Techniques with this approach are both self-supervised and internally trained, so no external training data is required. However, in such a training paradigm limited data are present for training machine learning models and the frequency content of the in-plane data may be insufficient to capture the true high-resolution image. In particular, the recovery of high frequency information is usually lacking. In this work, we show this shortcoming with Fourier analysis; we propose and compare several approaches to address the recovery of high frequency information. We test a particular internally trained self-supervised method named SMORE on N=10 subjects at three common clinical resolutions with three types of modification: frequency-type losses (Fourier and wavelet), feature-type losses, and low-resolution re-gridding strategies for estimating the residual. We find a particular combination to balance between signal recovery in both spatial and frequency domains qualitatively and quantitatively, yet none of the modifications alone or in tandem yield a vastly superior result. We postulate that there may be limits on internally trained techniques that such modifications cannot address, or limits on modeling SR as finding a map from low-resolution to high-resolution, or both.

ABSTRACT 21

The effect of perinatal and early-life exposure to metal mixtures on neurodevelopment

Naveen Chandra, A. Bhobe, A. Graves, B. Yeung-Luk, M. Kohr, S. Biswal, and F. Sille

Background and Objective: Accumulating evidence suggests that exposure to certain heavy metals contributes to neurobehavioral and cognitive deficits and may play a role in the pathogenesis of several neurodevelopmental disorders such as autism spectrum disorder (ASD). Metal toxicity increases the formation of reactive oxygen species (ROS) and can elevate oxidative stress in the nervous system. In the present study, we tested the hypothesis that perinatal and early-life exposure to PACC metal mixture (Pb, As, Cd, and CrVI) induces developmental neurotoxicity.

Methods: To test this hypothesis female C57BL/6J mice were exposed to PACC mixture 2 weeks preconception until weaning of the F1 generation at 3 weeks of age. The F1 offspring (4 weeks of age) underwent behavioral studies, including a Novel object recognition test [NOR] (learning and memory deficits) and an elevated plus maze [EPM] (Anxiety). At 5-6 weeks these mice were euthanized, and their brain slices were used for electrophysiology and brain and serum samples were used for molecular analysis.

Results: Our preliminary data reveals that PACC exposure at respective maximum contaminant levels (MCL) for Pb, As, Cd, or maximum action level (ACL) for Pb, has adverse effects on cognition and anxiety levels, as measured by NOR (decreased time in exploring a novel object) and EPM (decreased time in the open arm). Patch clamp recording from mPFC and hippocampus CA1 neurons in acute brain slices shows PACC metal exposure results in increased input resistance and intrinsic excitability. These physiological changes made PACC-exposed neurons enter into a hyperexcitable state.

Conclusions: Our study indicates that perinatal and early-life exposure to PACC metal mixture at supposedly "safe" drinking water levels leads to developmental neurotoxicity and potentially neurological disorders. Future studies will focus on transcriptomic analysis of brain tissues and pharmacological experiments to determine the mechanism underlying the PACC exposure effect.

ABSTRACT 22

Assembloid modeling using the oil-in-water droplet microtechnology

Kehan Ren, Ashleigh J. Crawford, Isha Bhorkar, David Schell, André Forjaz, Vasco Queiroga, Denis Wirtz

Cell-cell interactions and cell-extracellular matrix (ECM) interactions regulate cellular homeostasis in tissue and organ development, and dysregulation can result in disease. A variety of cell and tissue culture systems are commonly used to study these physiological and pathological processes; however, two-dimensional (2D) culture systems enable only partial capture of cell-cell interactions. The cellular heterogenicity, in situ architecture, and mechanical functions of the tissue microenvironment can only be accurately recapitulated in vitro using 3D systems, such as organoids. However, many organoid models are also limited to one cell type in one ECM or artificial cocultures of multiple cell types in the same ECM, which do not match the tissue anatomy. Many organoid models also experience significant size variation between organoids and introduce non-physiological crosstalk between organoids that form within the same well. Here, we present a protocol for generating multi-compartment assembloids, which are organoid models that incorporate multiple cell types and ECMs to match the tissue structure. The resulting assembloids are size-consistent, spatially controlled by the compartmentalized seeding of cells and ECM, and individually isolated to avoid organoid-organoid crosstalk. Realistic substrate stiffness, cell-ECM adhesion, and 3D cell interactions allow this assembloid model to accurately capture the architectural, molecular, and functional expression patterns of healthy tissues. Our protocol offers a robust alternative for modeling healthy and diseased tissues as a bridge between 2D cell culture and animal models.

ABSTRACT 23

Mathematical Modeling of Estrogen Regulation of Bone Remodeling

Ilia Rattsev, Casey Overby Taylor

Third-generation aromatase inhibitors (AIs) are considered superior to tamoxifen in treating early-stage hormone-receptor-positive breast cancer. However, up to 50% of patients develop aromatase inhibitor-induced musculoskeletal symptoms (AIMSS), such as osteoporosis and joint pain, which can reduce their quality of life and often lead to therapy discontinuation, resulting in worse outcomes. Aromatase is an enzyme that catalyzes the conversion of androgens to estrogens, constituting the primary source of estrogens in postmenopausal women. Inhibition of aromatase leads to complete depletion of circulating estrogen, which is a desirable effect in treatment of estrogen-sensitive tumors. While the bone-protective effect of estrogens is well-characterized, there exists a large variability in terms of AIMSS among women undergoing AI therapy, and prospective identification of patients at risk of experiencing toxicity is needed in the clinic. To better understand the complex effect of AI therapy on bone, we developed a mathematical model of estrogen regulation of bone remodeling. We used a previously established computational model of bone remodeling that describes the concerted action of osteoblasts and osteoclasts, mediated by T-cell and osteocyte signaling. In the current framework, we extend the previous model by incorporating the effect of estrogen on bone homeostasis via its regulation of RANKL, osteoclast apoptosis, and T-cell function. Our model accurately recapitulates the physiology of bone turnover and its regulation by estrogen and enables incorporation of genetic effects on the parameters. This work establishes the foundation for future systems pharmacology modeling of AIs, with the aim of personalized prediction of AI-induced bone toxicity.

ABSTRACT 24

DIMON: Learning Solution Operators of Partial Differential Equations on a Diffeomorphic Family of Domains

Minglang Yin, Nicolas Charon, Ryan Brody, Lu Lu, Natalia Trayanova, Mauro Maggioni

Learning solution operators of partial differential equations (PDEs) with neural networks, or neural operator, enables a novel paradigm for fast estimation of PDE solutions. However, there still lacks a rigorous framework that extends operator learning posed on a diffeomorphic family of domains without retraining. To address this need, we propose DIffeomorphic Mapping Operator learNing (DIMON), a general operator learning framework to approximate the PDE solution on a diffeomorphic family of domains by transporting the output of a latent operator posed on a reference domain via a diffeomorphism. The latent operator is approximated by a neural operator and parameterized by the transported input functions on the reference domain in conjunction with the shape parameter. We first provide a description of our framework, followed by three examples to demonstrate the utility of the framework in learning static and dynamic PDEs on both synthetic (rigid) and realistic (non-rigid) geometries. Examples include predicting the solution of the Laplace equation, reaction-diffusion equation, and a multiscale PDE that characterizes the electrical propagation on the left ventricles. This work paves the way toward fast prediction of a PDE solution on a family of domains and can facilitate the application of neural operators in engineering and medicine.

ABSTRACT 25

Navigating the Use of Patient-Reported Outcomes in Clinical Trials and Clinical Practice: The PROTEUS Consortium

Claire Snyder, Anne Schuster, Norah Crossnohere, Michael Brundage

There is increasing emphasis on incorporating the patient perspective in research and clinical care. Patient-reported outcomes (PROs) are patients' own reports of how they feel, function, and live their lives – and are measured using standardized, validated questionnaires. PROs can be included as endpoints in clinical trials and other research studies, with the results providing valuable information to clinicians, patients, and regulators for decision-making. Incorporating PROs in research studies requires specifying the methods appropriately, measuring the outcomes effectively, analyzing the data properly, and reporting the findings clearly – all so that the results can be translated into practice. PROs are also increasingly incorporated as part of routine care to screen for problems, monitor progress, and inform management. The use of PROs in clinical practice requires collecting the PRO data efficiently, communicating the PRO results usefully, interpreting the PRO scores meaningfully, and acting on the PRO findings effectively. The PROTEUS Consortium (Patient-Reported Outcomes Tools: Engaging Users & Stakeholders) helps navigate the use of PROs in both clinical research and patient care. The Consortium includes over 50 patient, clinician, research, health system, industry, policy, and regulatory groups from the US and internationally. Using the Knowledge-to-Action framework, PROTEUS partners with participants to disseminate and promote implementation of resources developed to optimize the use of PROs in research studies and patient care. Resources include articles, handbooks, users' guides, web tutorials, checklists, and templates – all of which are freely available at TheProteusConsortium.org.

ABSTRACT 26

Clinical Practice and Research Recommendations for Fever and Inflammation of Unknown Origin Based on a Modified Delphi Consensus Panel

William F. Wright, Lauren Stelmash, Albrecht Betrains, Catharina M. Mulders-Manders, Chantal P. Rovers, Steven Vanderschueren, and Paul G. Auwaerter

IMPORTANCE: Fever of unknown origin (FUO) and inflammation of unknown origin (IUO) continue to be commonly utilized medical diagnoses. Given the existing literature does not address the optimal contemporary diagnostic structures and evaluation processes for these conditions, developing a consensus set of recommendations would be useful for clinicians, researchers, and patients around the world.

OBJECTIVE: To develop expert-driven consensus recommendations on needed FUO and IUO research, clinical practice, education, and advocacy based on a modified Delphi technique.

EVIDENCE REVIEW: A 5-round modified Delphi process with data analysis was performed from October 2022 to July 2023. The process used an iterative Delphi technique and involved 4 rounds of online surveys and 2 live video conferences to achieve consensus among an expert member panel. RedCap, an online survey approach to conducting modified Delphi panels, was used. This panel consisted of international experts in adult fever and inflammation of unknown origin, or both, recruited by email from lists of prior peer-reviewed published studies and focused professional groups.

FINDINGS: Of 50 invited experts, 26 (52.0%) agreed to participate in the panel. Twenty-three panelists completed the first round of the survey, 21 completed round 2 and 3 of the survey, 20 completed round 4, and 7 participated in the round 5 live video discussions. Female panelist (n=6) completed all survey rounds. Consensus was reached on high-priority statements within 5 themes: (1) epidemiology (e.g., geographical location and travel history), (2) minimal diagnostic defining criteria, (3) evaluation, (4) classification of associated diseases, and (5) empirical therapy (e.g., antimicrobials, corticosteroids, and anti-inflammatory agents). Experts strongly disagreed with use of 18FDG-PET/CT as an important component of the diagnostic criteria for FUO. Moderate agreement was reached on the topics of importance to the site of temperature measurement, 3-week time-based criterion, need for a standard definition of relapsing fevers, and use of similar diagnostic approaches for both conditions.

CONCLUSIONS AND RELEVANCE: The findings of this qualitative study provide consensus-based recommendations for clinicians and highlight research gaps important to clinical care in FUO and IUO that are highly pragmatic as a guide for practice and research.

ABSTRACT 27

Large Language Models as combined quantitative and labeled data forecasters for Assured Autonomous Mechanical Ventilators

Nimeesha Chan, Anton Dahbura, Jim Fackler, Kimia Ghobadi

Patients who come into the ICU typically need some form of ventilatory support. The clinician needs to (1) analyze continuous and intermittent data streams, and only then (2) periodically, manually change the ventilator settings at the patient's bedside (an often risk-laden space). The overarching goal for this research is to develop methodologies that will deliver life-sustaining mechanical ventilation with both autonomy and trust, sufficient to assure the patient and their clinicians that the ventilator is being optimally adjusted to achieve patient outcomes that are equivalent, or superior to those achievable by clinicians alone. To design a trustworthy autonomous mechanical ventilation system, we built a flexible framework that combines Large Language Models (LLMs) and digital twins (DTs). In the first phase, the LLMs are used to predict univariate time series with clinical labels, which represent available multimodal patient data, and convey human-intuitive recommendations and predictions. Within the "sublanguage" designed for this LLM, a word signifies the state of the entire system at a single time point, across different data streams. Subsequent words generated are shown to be predictive of trend changes in the data and future system states. We tested this framework on 187 samples, each containing 250 observations, from one of five series within Monash's Australian Electricity Demand dataset, and achieved 0.13% MAPE. This study has the potential to reimagine how patient information is assessed and acted upon in the ICU, ultimately leading to more personalized, timely and effective patient care, and improved patient outcomes.

ABSTRACT 28

CCRL2 promotes malignant cell growth and induces STAT1 signaling in erythroleukemia

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Background: Developing targeted therapies in AML arising from antecedent MDS necessitates understanding of malignant cell growth pathways. The atypical chemokine receptor C-C chemokine receptor-like2 (CCRL2) is upregulated in CD34+ cells from MDS patients and secondary AML (sAML) blasts.

Aim: Identify secondary AML (sAML) groups with CCRL2 overexpression and dissect into the specific molecular pathway for CCRL2-mediated sAML growth.

Methods: Analysis of publicly available RNA-seq data (DepMap portal) and flow cytometry compared CCRL2 expression in various cell lines. CCRL2 expression was suppressed by CRISPR-Cas9. TF-1 erythroleukemic cells were engrafted in NSG mice. Doxycycline-inducible CCRL2 TF-1 cells were developed, through CCRL2 deletion by CRISPR-Cas9 followed by transduction with pLV-Puro-TRE-CCRL2/pLV-Hygro-CMV>tTS/rtTA expressing lentiviruses. Phospho-proteomics analysis was performed by mass spectrometry and analyzed by pathway enrichment analysis. Single cell transcriptomics analysis was performed in 3 paired samples from primary AML samples at diagnosis and at relapse after induction therapy and bone marrow transplantation.

Results: CCRL2 is overexpressed in AML cell lines with erythroid and differentiation. CRISPR-Cas9 CCRL2 deletion suppressed the growth and clonogenicity of TF-1 and K562 cells in vitro and growth of TF-1 cells in vivo. Doxycycline-induced CCRL2 expression increased TF-1 cells growth. Unbiased phospho-proteomics analysis showed that IFNγ/STAT1 signaling, and particularly STAT1 and STAT1-targets IFIT1, IFIT3 and ISG15 is the top CCRL2-regulated pathway in erythroleukemia. Single cell study showed that CCRL2 and STAT1-targets are overexpressed in malignant erythroid progenitors enriched in relapsed samples from AML patients.

Conclusion: CCRL2 promotes cell growth in erythroleukemia, potentially through STAT1 activation and transcriptional activity, endorsing the therapeutic potential of CCRL2/STAT1 targeting in erythroleukemia.

ABSTRACT 29

TRBC1-targeting antibody drug conjugates for the treatment of T-cell cancers

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Patients suffering from T-cell cancers have short survival and limited therapeutic options due to the lack of antigens that effectively discriminate tumor from normal T cells. A significant proportion of T-cell neoplasms express the αβ T cell receptor (TCR) on their cell surface. An αβ T cell, healthy or neoplastic, selects one of two possible T cell receptor β-chain constant region (TRBC) alleles: TRBC1 or TRBC2 during somatic recombination. Neoplastic αβ T cells uniquely express either TRBC1 or TRBC2 TCRs due to clonal outgrowth. Therefore, targeting either the TRBC1 or TRBC2 protein expressed in cancer can spare enough healthy T cells to preserve immune function. However, the first-in-human clinical trial of anti-TRBC1 CAR T cells reported limited efficacy and persistence of CAR T cells. Here, we demonstrate that anti-TRBC1 CAR T cells can be reciprocally killed by normal TRBC1+ T cells upon binding, hindering their efficacy to fight cancer. To develop an alternate therapy, we engineered an anti-TRBC1 targeted antibody drug conjugate (ADC) to selectively deliver SG3249 to TRBC1+ cells. Anti-TRBC1-SG3249 could selectively kill TRBC1+ cells in vitro and also cured mice with disseminated TRBC1+ cell-line and patient-derived xenografts. Our work demonstrates that ADCs may be the optimal therapeutic modality for TRBC1-targeting and provide better outcomes for patients suffering with T-cell cancers.

ABSTRACT 30

Developing an affordable, miniaturized microscope for non-invasive point-of-care blood cell diagnosis

Mantej Singh

Accurate assessment of red blood cell (RBC) morphology and white blood cell (WBC) count is critical for diagnosing infections, sepsis, and sickle cell disease. However, current methods such as blood draws are often expensive, cannot be used on neonates, and impractical for point-of-care use, particularly in low-resource settings. To address this challenge, we are currently developing Popsicam —a cost-effective, miniaturized microscope designed for non-invasive imaging of blood cells in sublingual vasculature.

Utilizing oblique-back illumination and miniaturized optics, Popsicam achieves high-speed, high-resolution imaging of human microvasculature in vivo. By capturing dynamic videos of blood cells under the tongue, and using advanced optical and computational techniques, we aim to provide real-time visualization, morphological analysis, and cell counting of RBCs and WBCs. Leveraging open-source electronics like Raspberry Pi and affordable optics, Popsicam stands out as a cost-effective and user-friendly solution suitable for bedside use in diverse healthcare settings.

While our initial focus is on creating an essential diagnostic tool for sickle cell disease, Popsicam's versatility extends its applications to a wide range of hematological conditions. This innovation not only addresses the limitations of existing diagnostic methods, but also presents a transformative approach to non-invasive, point-of-care blood cell diagnostics. Popsicam's cost-effectiveness and user-friendly design make it particularly impactful in resource-constrained environments, addressing the limitations of traditional diagnostic methods and contributing to improved healthcare accessibility and affordability. Popsicam holds the potential to revolutionize hematological assessments, offering timely and comprehensive information for informed clinical decision-making.

ABSTRACT 31

Overcoming limitations of Raman spectroscopy for biomedical applications

Piyush Raj, Ishan Barman

Raman spectroscopy has shown promise in conducting non-invasive in vivo imaging of cellular and tissue biochemical components without compromising internal structures or functionality. However, its widespread application in biology is limited due to weak signals, slow acquisition rates, shallow penetration depth, and spectral congestion. During my graduate study, I have proposed methods to address each of the mentioned limitations. The problem of weak signal and spectral congestion is addressed using novel class of Raman reporter targeting tumor cells overexpressing furin which were tested in cell culture and mouse model study. The issue of shallow penetration depth was addressed through hardware modifications by collecting signal at offset location. Spatially offset Raman spectroscopy was used to enhance signal collection from deeper layer. The proposed method provided a comprehensive understanding of osteoarthritis (OA) of articular cartilage by accurately predicting cartilage health and providing damage gradation associated with molecular changes. The limitation of slow acquisition speed was partially solved by the use of compressive sensing algorithm bringing down acquisition time by more than 10-fold in certain cases. Finally, we also proposed a new measurement platform to do reliable concentration prediction of biomolecules with surface-enhanced Raman spectroscopy. We were able to quantify TSH levels on patient sample across different days and substrates.

ABSTRACT 32

Early Palliative Care Engagement by Screening Implemented by the Emergency Department's Care Coordination Team – A Pilot Program

Balakrishna Vemula, Razeen Karim, Danielle Doberman

Background: Our healthcare system serves a significant number of patients who struggle with serious illness

and have unmet palliative care (PC) needs. Some of these unmet needs include uncontrolled

symptoms, understanding their prognosis, developing long term goals, and optimizing quality of life. Although the Emergency Department (ED) offers a unique setting to provide early palliative care, staffing limitations curtail hospitals from establishing ED-palliative partnerships.

Methods: A clinical decision support tool was created to identify patients with treatment/code status limitations and prompted a care coordination referral. Care coordinators screened patients for unmet palliative needs using a content-validated screening tool and consulted palliative care for positive screens. Feasibility of this two-step ED-palliative screening protocol was defined by two criteria: a ≥ 50% increase in palliative consults originating from the ED and a ≥ 50% consultation completion rate for patients who screened positive for unmet palliative needs.

Results: Palliative care consultations originating from the ED increased by 110% from 32 to 67 consultations, and 57% (40/70) of patients who screened positive for unmet palliative needs received a consultation.

Conclusion: Our project demonstrated feasibility of a two-step ED-palliative protocol by increasing palliative care consultation without necessitating additional staff.

Key Message: Palliative care screenings in the ED focus on either manual screening limited by staffing constraints or clinical decision support limited by data within the electronic health record. Our novel protocol utilizes both methods to mitigate these limitations. We demonstrated feasibility by increasing palliative consultations in the ED without staffing constraints.

ABSTRACT 33

A Cross-Sectional Study on Electrocardiographic Changes In Chronic Kidney Disease Patients in A Tertiary Care Hospital

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Background: People with CKD are five to ten times more likely to die prematurely than they are to progress to end stage kidney disease. Cardiovascular disease is a major cause of mortality and morbidity among patients with CKD. More than 50 percent of patients with CKD die due to cardiovascular complications. In addition to the traditional risk factors such as coronary disease, diabetes, and left ventricular hypertrophy, patients with ESRD have an increased risk of mortality due to electrolyte disturbances, acid-base balance, and plasma volume shifts that occur during haemodialysis.

Methods: 70 patients with CKD were included to study the electrocardiographic changes in patients with chronic kidney disease attending the outpatient clinic of Kempegowda Institute of Medical Sciences, Bangalore,India.

Results: 47% of the study participants belonged to the age group between 51-60 years of age. The mean age of the study participants was found to be 54.11+8.46 years. Majority of the study participants had diabetes (86%) and hypertension (61%). 64% of the study participants had stage 3 CKD. 23% of the study participants had left ventricular hypertrophy with 16% of study participants having ischemic changes in ECG. When ECG changes were associated with Stages of CKD, association was found to be statistically significant between left ventricular hypertrophy as well as ischemic changes in CKD patients and stages of CKD of the study participants.

Conclusion: Earlier screening of CKD patients is recommended. The changes in ECG of patients with CKD can aid in detection of CVD and should be carried out in all patients with CKD which may positively impact the care of the CKD population by permitting improved targeting of cardiovascular risk reduction strategies. Future studies are recommended to add additional cardiac work-up such as stress testing or cardiac/coronary computed tomography scanning to ECG.

ABSTRACT 34

Stand in Surgeon's Shoes: Virtual Reality Cross-training to Enhance Teamwork in Surgery

Benjamin D. Killeen, Han Zhang, Liam J. Wang, Zixuan Liu, Constantin Kleinbeck, Michael Rosen, Russell H. Taylor, Greg Osgood, Mathias Unberath

Teamwork in surgery depends on a shared mental model of success, i.e. a common understanding of objectives. A shared model leads to increased engagement among team members and is associated with fewer complications and overall better outcomes for patients. However, clinical training typically focuses on role-specific skills, leaving individuals to acquire a shared model indirectly through on-the-job experience. Here, we investigate whether cross-training can enhance a shared mental model more directly. Leveraging virtual reality (VR), we evaluate a curriculum in which surgeons and non-surgeons swap roles inside a realistic VR operating room. Our study focuses on X-ray guided pelvic trauma surgery, a procedure where successful communication depends on the shared model between the surgeon and a C-arm technologist. We find that exposing non-surgeons to VR surgical training results in higher engagement ($p < 0.001$) with the C-arm technologist role. It also has a significant effect on non-surgeon's mental model of the overall task; novice participants' estimation of the mental demand and effort required for the surgeon's task increases after training, while their perception of overall performance decreases ($p < 0.05$), indicating a gap in understanding based solely on observation. As workflows grow increasingly sophisticated, we see VR cross-training as being able to directly foster a shared model for success, ultimately benefiting patient outcomes through more effective teamwork in surgery.

ABSTRACT 35

Inconsistent MR acquisition in longitudinal volumetric analysis: impact and solution

Lianrui Zuo, Savannah Hays, Blake Dewey, Samuel Remedios, Yuan Xue, Sandra Cassard, Carolyn Koch, Ann Fishman, Aaron Carass, Jerry Prince, Ellen Mowry, Scott Newsome

Magnetic resonance imaging (MRI) has been routinely used in diagnosis and monitoring disease activity for people with multiple sclerosis (MS). Variability in imaging protocols across different sites, despite the international guidelines for standardization, leads to contrast variations in MRI scans, affecting multi-site longitudinal analysis. This study investigates the impact of these inconsistencies in MRI images across multiple sites and assesses the effectiveness of image harmonization as a solution. Specifically, we conducted and compared three parallel volumetric analyses based on MR images from a single reference site, unharmonized images from eight sites, and harmonized images from eight sites. In each analysis, a linear mixed effect model was applied to study the statistical relationship between age and brain cortical gray matter volume. The results indicated significant improvements in intra-class correlations and residual variance after harmonization, bringing consistency on par with single-site data. The study highlights the importance of standardized image acquisition in MS research. Moreover, variation persists even for sites following the guideline. Lastly, we demonstrate that harmonization can significantly mitigate the effects of acquisition variability, ensuring more reliable longitudinal volumetric analysis for people with MS.

ABSTRACT 36

Comparison of treatment non-responders versus responders in ATTR-CM

Yazan Alshawkani, Bairavi Shankar, Lisa Yanek, Artrish Jefferson, Daniel Tsottles, Serena Zampino, Jennifer Barranco, Abby Hubbard, Mark Ranek, Kavita Sharma, Michael Polydefkis, Joban Vaishnav

Background: Current treatments for transthyretin amyloid cardiomyopathy (ATTR-CM) aim to diminish clinical deterioration. There are limited real-world data on treatment response in ATTR-CM.

Methods: Patients seen at the Johns Hopkins University Comprehensive Amyloidosis Center with ATTR-CM on treatment for ≥6 months with a stabilizer or silencer were included for analysis. Clinical non-responders (NR) met at least one clinical (≥1 HF hospitalization or acute visit, ≥50% increase in loop diuretic dose, or increase in NYHA class) and one biomarker/imaging endpoint (≥30% increase in NT-proBNP, ≥30% decrease in eGFR, or ≥10% decrease in LVEF). Characteristics were compared between NR and responders (R) using Chi-square test, Fisher's exact test, or Mann-Whitney U test.

Results: Of 135 patients, 52 (39%) were NR. NR compared to R were more likely Black (72.5% v 27.4%), hereditary (63.3% v 43.2%) and had prior HF hospitalization (57.1% v 21.1%), higher diuretic dose (71.81 ± 75.00 v 38.30 ± 24.50 mg), lower eGFR (52.60 ± 20.80 v 66.18 ± 20.20 mL/min/1.73 m2), higher troponin I (0.12 ± 0.10 v 0.08 ± 0.10 ng/mL), and lower LVEF (41.6% v 50.7%), $p<0.05$. NR had significantly increased risk for death over the follow-up period ($p=0.01$).

Conclusion: We find nearly one-third of ATTR-CM patients on treatment have disease progression. Non-responders were more likely Black, with hereditary disease, had advanced disease features, and had significantly worse survival compared to responders. Early identification of treatment non-response and novel therapeutics are pivotal to improving outcomes in ATTR-CM.

ABSTRACT 37

Elucidating the mechanism behind IL-7 potentiation by a neutralizing anti-cytokine monoclonal antibody

Emily Ariail, Paul Sargunas, and Jamie Spangler

IL-7 is a cytokine that plays a critical role in immune cell proliferation, survival, function, and homeostasis. Anti-cytokine antibodies have been identified for many common cytokines such as IL-2, IL-4, and IL-7. It has been discovered that the anti-IL-7 antibody, M25, potentiates the bioactivity of the cytokine, but the mechanism behind this remains largely unknown. To elucidate this mechanism, we have solved the crystal structure of the IL-7/M25 complex and conducted studies investigating its biophysical and pharmacokinetic properties. Our results indicate that M25 potentiates the activity of IL-7 through more than one distinct mechanism, including half-life extension and facilitated diffusion via γC receptor competition. This work provides unprecedented insight into the mechanism behind IL-7 potentiation, which will contribute to a better understanding of other potentiating anti-cytokine antibodies and create new opportunities for biotherapeutic development.

ABSTRACT 38

Regulation of Stress Granules by O-GlcNAcylation in Stressed and Ischemic Cardiomyocytes

Hannah Swimm, Wenxi Zhang, Yashas Mallikarjun, Deepthi Ashok, D. Brian Foster, Brian O'Rourke, Natasha E. Zachara, & Kyriakos N. Papanicolaou

Background: Stress granules (SGs) are cytoplasmic ribonucleoprotein condensates that form during stress. SGs protect cells by rewiring translation and sequestering signaling proteins. Previous research found that SG formation requires the protein modification, O-GlcNAcylation. SGs are implicated in neuronal dysfunction, but their role in cardiac pathophysiology is unexplored. In the present work, we investigated if SGs form in cardiomyocytes during chemical induction or ischemia and whether manipulation of O-GlcNAcylation affects this.

Methods: We developed an adenovirus encoding a fusion protein of GFP with G3BP1, an RNA-binding protein essential for SG formation. This was expressed in H9c2 cells and monitored by confocal microscopy after sodium arsenite addition. CellProfiler was used to quantify SG formation. Cells were treated with inhibitors of OGT (O-GlcNAc Transferase) and OGA (O-GlcNAcase) which add and remove O-GlcNAc. Additionally, we employed siRNA knockdown of these enzymes. In another experiment, we applied a coverslip onto primary cardiomyocytes to induce acute hypoxia and nutrient deprivation, simulating ischemia.

Results: We observed SG formation in SA-treated H9c2 cells that was reduced by OGT inhibition and knockdown. However, OGA inhibition or knockdown did not alter this. Additionally, we observed the formation of SGs exhibiting O-GlcNAc immunoreactivity in cardiomyocytes following coverslip application.

Conclusions: O-GlcNAcylated proteins are recruited in cardiomyocyte SGs after chemical induction and during simulated ischemia. Baseline O-GlcNAcylation is necessary for SG formation, but further elevating O-GlcNAcylation does not enhance SG formation. This highlights the complexity of cardiomyocyte SG dynamics, whereby O-GlcNAcylation could be implicated in assembly and disassembly.

ABSTRACT 39

Is Dependent Cannabis Use In Adult Hospitalizations With Inflammatory Bowel Disease Associated With Major Adverse Cardiovascular And Cerebrovascular Events? Insights From National Inpatient Sample Analysis, 2020

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Background: Inflammatory bowel disease (IBD) and dependent cannabis use or cannabis use disorder (CUD+) are independent risk factors for cardiovascular diseases. Usage of cannabis for pain increased in IBD patients. However, associated cardiovascular safety remains unclear. This study aims to investigate the major adverse cardiac and cerebrovascular events (MACCE) associated with CUD+ in hospitalized IBD patients.

Methods: We analyzed the National Inpatient Sample 2020 using ICD-10-CM codes; hospitalized IBD patients were identified and divided based on CUD's presence or absence. Multivariable regression models were performed to evaluate MACCE [in-hospital mortality, acute myocardial infarction (AMI), cardiac arrest (CA), and acute ischemic stroke (AIS)] odds after adjusting for baseline demographics, hospital-level characteristics, and relevant cardiac/extra-cardiac morbidities.

Results: Among the 302,770 hospitalized adult IBD patients, 3.1% (9,490) had CUD+. The majority of patients in the CUD+ cohort were white (67.7%), male (57.5%), and aged between 18 and 44 years (66.2%). Cardiovascular risk factors like hypertension, diabetes, hyperlipidemia, and prior myocardial infarction were higher in the CUD- cohort ($p< 0.001$) compared to the CUD+ cohort. The CUD+ cohort had a lower rate of MACCE (3.1% vs. 5.8%), crude in-hospital mortality (0.7% vs. 2.2%), AMI (1.7% vs. 2.6%), CA (0.3% vs. 0.7%), and AIS (0.6% vs. 1.2%) with statistical significance ($p<0.001$). However, after adjusting for baseline characteristics and comorbidities, the adjusted odds ratios (aORs) did not show a statistically significant difference for MACCE (aOR: 0.9, 95%CI 0.65-1.25, $p = 0.530$), CA (aOR: 0.54, 95% CI 0.2-1.47, $p = 0.227$), and AIS (aOR: 0.86, 95% CI 0.43-1.73, $p = 0.669$).

Conclusion: Our study did not find a statistically significant difference in MACCE among hospitalized IBD patients with and without CUD. This emphasizes the need for more extensive prospective studies focusing on the quantity, method, and duration of cannabis use (recreational or chronic habitual) in patients with IBD.

ABSTRACT 40

Safety and PK/PD of A Tenofovir Rectal Douche Administered in Different Sequences (DREAM-03)

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On-demand and behaviorally congruent forms of HIV pre-exposure prophylaxis (PrEP) have long been requested by communities at risk of HIV, especially men who have sex with men (MSM). DREAM-03 sought to report safety and PK/PD outcomes when using multiple tenofovir (TFV) douches with and without water douches in three sequences: (A) three TFV douches, (B) one TFV douche then two tap water douches, and (C) two tap water douches then one TFV douche. We collected blood over 168 hours and rectal biopsies over 72 hours. TFV and TFV diphosphate (TFV-DP) were quantified using validated methods. Anti-HIV effect was evaluated using an ex vivo explant HIV challenge method with biopsies collected over 6 hours. An HIV p24 assay was used to quantify viral replication. In total, nine adult male participants were enrolled. No grade >2 study related adverse events were reported. Plasma TFV concentrations at 4 and 6 hours were significantly higher in sequence A than those in sequence B. A trend of higher TFV-DP concentrations in rectal mucosal mononuclear cells at 24 and 72 hours in sequences A and C than those in sequence B were also observed. Compared to pre-drug baseline, approximately one log reduction of HIV replication after ex vivo HIV challenge were observed in all sequences . Our result demonstrates that administering three TFV rectal douches are well tolerated. In addition, using non-medicated douches after a TFV douche may likely reduce both systemic and local TFV exposures, and may subsequently compromise anti-HIV effect of the TFV douche.

ABSTRACT 41

Bivalent mRNA COVID Vaccines Elicit Predominantly Cross-reactive CD4+ T cell Clonotypes

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Background: The emergence of the Omicron BA.5 sublineage in February 2022 raised concerns due to its ability to escape neutralizing antibodies induced by ancestral spike mRNA vaccines and natural infection with prior SARS-CoV-2 variants. Bivalent COVID-19 vaccines, containing mRNA for both ancestral and Omicron BA.5 spike proteins, were developed to enhance immune responses against the BA.5 suvlineage. However, studies have shown that these bivalent vaccines do not induce stronger T cell responses to the BA.5 spike protein than monovalent vaccines containing only ancestral spike mRNA. We tested the hypothesis that this was due to the preferential expansion of cross-reactive memory T cells rather than naive BA.5 mono-reactive T cells.

Methods: We used the ELISpot assay to determine the targeted epitopes and the functional expansion of specific T Cells (FEST) assay to assess the percentage of CD4+ T cells that cross-recognized both ancestral and BA.5 spike proteins compared to those that were mono-reactive for each protein. We conducted this analysis in two distinct cohorts: 20 healthy donors (HDs) and 20 people living with HIV (PLWH) on suppressive antiretroviral therapy. All the participants received either the Pfizer-BioNTech (BNT162b2) or Moderna (mRNA-1273) SARS-CoV-2 ancestral spike/BA.5 spike bivalent vaccine.

Results: We found robust T cell responses to both ancestral and BA.5 spike proteins in both HDs and PLWH. Importantly, the FEST assay revealed that a predominant percentage of these responses were cross-reactive CD4+ T cells. Specifically, only 8.9% and 3.8% of spike-specific CD4+ T cell receptors were mono-reactive to BA.5 spike protein in HDs and PLWH respectively.
Additionally, we conducted an in-depth analysis of the individual ancestral spike protein epitopes targeted by T cells in bivalent vaccine recipients. We found that more than 80% of these epitopes were ones that did not contain BA.5 mutations.

Conclusions: In conclusion, our study suggests that the current bivalent vaccines do not effectively induce substantial BA.5-mono-reactive T cell responses; instead, cross-reactive T cells dominate the spike-specific T cell response. These findings have significant implications for future COVID vaccine strategies.

ABSTRACT 42

Understanding and Tackling (dis) Information Agents - A Case of Crisis Informatics

Nikhil Sharma, Ziang Xiao

Access to trustworthy information to the masses is crucial for managing crisis and disaster events such as the pandemic. However, the urgency and criticality to gain information during the formative stages of the crisis leads to the spreading of disinformation which often leads to panic, distrust in trustworthy sources, and even loss of life. As seen during the pandemic, we are woefully underprepared for disinformation wars leading to mass persuasion. This risk is further amplified by the coming of personalized conversational AI which has the potential to increase the spread and potency of disinformation manyfold. In this work, we 1) critically analyze and measure the true feasibility of conversational agents to be used as disinformation agents and 2) create and test methods to mitigate this risk. In the first phase of our study, we found that participants engaged in more biased information querying with LLM-powered search, and an opinionated LLM reinforcing their views exacerbated this bias.

ABSTRACT 43

Computational Approaches to Understanding Surgical Videos: The Case of Cataract Surgery

Nikhil Sharma, Daniel Khashabi, Swaroop Vedula, Shameema Sikder

Recently, AI agents have gained the ability to process and understand multimodal inputs that might be able to address the issue of expert feedback at scale. Our work diverging from conventional applications of such agents limited to identification tasks, ventures instead into the realms of long-form reasoned narratives that evaluate and critique the observed actions to generate expert-level feedback for surgeons.

In this work, we, 1) define properties of expert narratives 2) benchmark SOTA vision-language models on medical narrative generation, 3) test Large Language Model bootstrapping methods to generate inferred narratives and 4) evaluate the gap in expert narratives and model-produced narratives.

We evaluated 3 model families (9 models x 3 methods) on 19 videos capturing the rhexis phase of cataract surgery with our 7-tier evaluation framework (JH-CEQBank). Overall, we found that bootstrapping VLM outputs with LLM, scaling models, and contextualizing the prompts improved the quality of generated narratives. However, the gains regardless of the method were concentrated around earlier tiers.

ABSTRACT 44

A Comparative Study of Tumor Synthesis in Abdominal Computed Tomography: Reader Studies, Technology Trends, Case Studies, and Future Promises

Qi Chen, Yuxiang Lai, Xiaoxi Chen, Qixin Hu, Alan Yuille, Zongwei Zhou

Computer-aided tumor detection, empowered by artificial intelligence (AI), holds great promise in improving the efficiency and accuracy of interpreting over 40 million CT scans performed annually in the United States. However, this promise confronts a significant challenge: only a few CT scans contain tumors and even fewer present early-stage tumors. Developing AI using real tumors often encounters the bottleneck of data scarcity, annotation difficulty, and low prevalence of early (small) tumors. Alternatively, tumor synthesis offers a solution to overcome these constraints by generating extensive tumor examples in medical images, which are valuable for training AI models for tumor detection/segmentation. Successful tumor synthesis must generate realistic synthetic tumors that can be generalizable to various organs. After a comprehensive review of the state-of-the-art tumor synthesis approaches across multiple diseases and organs, this paper presents current research progress and analyzes key defining properties of two prominent technology trends. Firstly, modeling-based approaches, exemplified by Pixel2Cancer, can simulate tumor development over time in CT scans based on a set of generic rules. Secondly, learning-based approaches, exemplified by DiffTumor, can learn from only a few annotated tumor examples in one organ and generate synthetic tumors in other different organs. Reader studies involving three expert radiologists indicate that our synthetic tumors are convincingly realistic---even professionals can mistake them for real tumors. More importantly, three case studies in the liver, pancreas, and kidneys demonstrate that AI trained on synthetic tumors can achieve performance comparable to (or even higher than) that obtained by AI trained on real data for early tumor detection. Tumor synthesis, both high-risk and high-payoff, has substantial future promises to expand datasets, enhance AI reliability, and improve tumor detection performance. Finally, to keep pace with rapid advancements in tumor synthesis, we intend to regularly update a collection of relevant papers and their open-source implementations at https://github.com/MrGiovanni/SyntheticTumors/blob/main/AWESOME.md.

ABSTRACT 45

LNCRNA-Pre-MRNA Interaction Mediated Suppression of Amino Acid Catabolism In Fatty Liver Diseases

Marcos Emmanuel Jaso Vera, Shohei Takaoka, Xiangbo Ruan

Non-alcoholic fatty liver disease (NAFLD) is increasing worldwide and impaired amino acid (AA) metabolism in the liver has recently emerged as a hallmark of this disease. Decreased expression of genes in the AA catabolism pathways can result in the accumulation of AA and ammonia, which increase liver damage and development of NAFLD and steatohepatitis (NASH). A molecular mechanism for AA catabolism dysregulation in NAFLD is unknown. We identified a non-conserved, liver-specific human long non-coding RNA (lncRNA), hLMR1 (Gene symbol: LOC100507389), which promotes cholesterol synthesis. We obtained preliminary data suggesting a novel regulatory mechanism of catabolic AA gene expression mediated by lncRNA-pre-mRNA interaction by performing RNA-seq analysis in humanized livers and Chromatin isolation by RNA purification (ChIRP) assay. Defining this mechanism and its factors may provide new therapeutic strategies for NAFLD.

To explore the hLMR1-mediated suppression of AA catabolism in diseases, we analyzed published RNA-seq data using human liver tissues from healthy individuals or NAFLD patients. We found that genes in the AA catabolism pathway were down-regulated during NAFLD and NASH, while the expression of hLMR1 increased. In the luciferase reporter assay, hLMR1 suppressed the reporter activity depending on pre-mRNA sequences of AA catabolism genes. Furthermore, overexpression of hLMR1 in primary human hepatocytes decreased the expression of AA catabolism genes. These data suggest that hLMR1-mediated suppression of amino acid catabolism may contribute to the development of NAFLD. Our future work will test the role of hLMR1 in suppressing AA catabolism in vivo using traditional and humanized liver mouse models.

ABSTRACT 46

A Finite Element Analysis of Alternative Laminectomy Procedures

Craig Almeida, Alexandra Seidenstein, Amit Jain, Jill Middendorf

Lumbar stenosis often requires laminectomy procedures, yet these surgeries carry the risk of complications such as spondylolisthesis due to pars interarticularis (PI) fractures. Less invasive alternatives, like laminotomies preserving more lamina than full laminectomies, have emerged. Finite element (FE)models assess the risk of PI fractures by evaluating PI stress during spinal motions. This study aims to distinguish differences in PI stress between low bone removal(Unilateral Laminotomy, ULO, Bilateral Laminotomy, BLO)and high bone removal procedures(Hemilaminectomy, HL, Full Laminectomy, FL). Using an FE model of a 49-year-old female L1-L5 spine, simulations for ULO, BLO, HL, and FL were conducted and compared. Each procedure removed approximately 25% of the L4-L5 facet joint, preserving at least 6 mm of the L4 pars. Additionally, 12 variations of ULO were simulated by varying pars width and face joint area. Each variation of the procedures was validated by the clinical author. Compressive follower loads and torsional loads were applied to simulate flexion, extension, lateral bending, and axial rotation. PI stress, Facet joint forces and range of motion (ROM) were analysed. ROM did not vary significantly among the 4 procedures. PI Stress increased progressively with increased resection. PI stress approached and exceeded the ultimate stress of bone after reducing pars thickness below 5 mm. Although pars stress doesn't reach bone failure levels in the four cases, patient-specific factors and disc degeneration could elevate risks. Given the reduced risk of pars fracture with ULO and BLO, surgeons should consider these alternatives over HL and FL for treating spinal stenosis.

ABSTRACT 47

Leveraging AI Predicted and Expert Revised Annotations in Interactive Segmentation: Continual Tuning or Full Training?

Tiezheng Zhang, Xiaoxi Chen, Chongyu Qu, Alan Yuille, Zongwei Zhou

Interactive segmentation, an integration of AI algorithms and human expertise, premises to improve the accuracy and efficiency of curating large-scale, detailed-annotated datasets in healthcare. Human experts revise the annotations predicted by AI, and in turn, AI improves its predictions by learning from these revised annotations. This interactive process continues to enhance the quality of annotations until no major revision is needed from experts. The key challenge is how to leverage AI predicted and expert revised annotations to iteratively improve the AI. Two problems arise: (1) The risk of catastrophic forgetting---the AI tends to forget the previously learned classes if it is only retrained using the expert revised classes. (2) Computational inefficiency when retraining the AI using both AI predicted and expert revised annotations; moreover, given the dominant AI predicted annotations in the dataset, the contribution of newly revised annotations---often account for a very small fraction---to the AI training remains marginal. This paper proposes Continual Tuning to address the problems from two perspectives: network design and data reuse. Firstly, we design a shared network for all classes alongside class-specific networks dedicated to individual classes. To mitigate forgetting, we freeze the shared network for previously learned classes and only update the class-specific network for revised classes. Secondly, we reuse a small fraction of data with previous annotations to avoid over-computing. The selection of such data relies on the importance estimate of each data. The importance score is computed by combining the uncertainty and consistency of AI predictions. Our experiments demonstrate that Continual Tuning achieves a speed 16 times greater than repeatedly training AI from scratch without compromising performance.

ABSTRACT 48

Characterizing polygenic risk scores among a breast cancer cohort in the All of Us program

Tamisha Dzifa Segbefia

Background: Breast cancer (BC) is one of the leading causes of cancer deaths among women, accounting for over 570,000 deaths worldwide in the US. However, researchers are working to develop models that can accurately predict breast cancer risk. BC studies have shown that the published 313 variant-based BC polygenic risk score (PRS_313) has predictive ability to determine whether a patient is at risk of breast cancer. This study aims to calculate polygenic risk scores among a breast cancer and control cohort in the All of Us (AoU) research program.

Methods: We applied a validated BC phenotype and identified 6,755 AoU research participants. Our working sample included a random selection of 5,000 women with BC from the AoU program. We created a data processing pipeline to link demographic, genomic, and clinical characteristics of patients data, and to calculate the PRS for each patient in the cohort.

Results and Conclusions: We describe the distribution of PRS among this cohort and the proportion that has at least one of the 313 variants. Findings add to our understanding of risk variance present in the AoU cohort.

ABSTRACT 49

Immune checkpoint inhibitor TIGIT ligands CD155 and CD112 increase during acute kidney injury

Shishir Patel, Radhika Kapoor, Qisen Guo, Mahta Gooya, Hamid Rabb & Sanjeev Noel

Background: We recently demonstrated that emerging immune checkpoint inhibitor T cell immunoreceptor with Ig and ITIM domains (TIGIT) increased in kidney T cells and mediated acute kidney injury (AKI) in mice. However, the identity and role of TIGIT ligands in AKI is unknown. In this study we examined TIGIT ligands, CD155, CD112 and CD113 during AKI.

Methods: WT mice underwent bilateral IR injury and CD155, CD112 and CD113 were assessed 1 day (24h) or 18 days post AKI with western blotting. Flow cytometry was performed to identify cells that express TIGIT ligands at baseline and 24h after IR injury. In-vivo blocking experiment were performed using anti-CD155 (250mg/mouse, single dose) and anti-TIGIT (4D4, 1B4 and 1G9, 100mg/mouse, three doses) antibodies and effect on kidney function was assessed by evaluating serum creatinine (SCr) levels.

Results: Western blotting showed enhanced kidney expression of CD155 (5.6□0.5 fold; P<0.001) and CD112 (2.4□0.5 fold; P<0.01) 24h after AKI compared to baseline. At 18 days, CD155 expression returned to basal levels however, CD112 remained elevated. CD113 expression was reduced 24h after AKI (0.7□0.2 fold; P=0.04) with restoration at 18 days. Flow analysis showed CD155 expression mainly by CD4, DN, NKT cells at baseline. Post AKI, CD155 expression increased significantly in CD11b+ cells (4.1□1.4% vs 0.1□0.04%; P<0.001), compared to control. CD112 was significantly expressed by NKT and CD19-CD11b- cells and further increased after IR injury. In-vivo anti-CD155 antibody treatment had no effect on SCr following AKI, compared to isotype control mice. TIGIT blocking antibody, 4D4, showed significant reduction (2.1±0.5 md/dL vs 3.4±0.4 mg/dL) in SCr at 48h following IR injury (P<0.01).

Conclusion: TIGIT ligand CD155 and CD112 expression increases following AKI in CD11b+ and NKT cells, respectively. Targeting TIGIT is a promising novel therapeutic approach for AKI

ABSTRACT 50

Inducible deletion of transcription factor Nrf2 in the renal proximal tubule after severe acute kidney injury modifies repair and fibrosis

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Background: The Nrf2-dependent antioxidant and anti-inflammatory system plays a protective role in preventing experimental AKI. However, most patients are seen after AKI, and severe AKI leads to CKD. The role of Nrf2 in recovery from AKI and progression to CKD is not known.

Methods: Wild type and proximal tubule Nrf2 specific tamoxifen-inducible conditional knockout (SLC34a1Nrf2 KO) mice were subjected to severe unilateral ischemia (45 minute) reperfusion injury (UIRI). Tamoxifen (200mg/Kg) treatment was initiated after reperfusion (0h), 24h and 48h after UIRI to delete the Nrf2 gene. Mice were euthanized at day 10. Kidney tissue was evaluated for fibrosis using Mason's trichrome staining, pro-fibrotic gene expression using qPCR and immune cell profiling using flow cytometry.

Results: Tamoxifan treatment resulted in kidney Cre expression. Histological scoring of Mason's trichrome stained kidney sections revealed significantly higher fibrosis in the outer medullary region of SLC34a1Nrf2 KO mice compared to WT counterparts (9.85□4.13 vs 3.55□0.98; p=0.04). In renal cortex, fibrosis trended towards being higher in SLC34a1Nrf2 KO mice compared to WT mice but was not statistically significant (8.6□4.41 vs 2.95□2.66, p=0.10). Kidneys of SLC34a1Nrf2 KO mice had an increased mRNA expression of pro-fibrotic mediator TGF□ compared to WT counterparts (1.37□0.26 vs 0.60□0.41-fold change, p=0.03). Furthermore, kidneys of SLC34a1Nrf2 KO mice had significantly increased percentage of CD45+ immune cells (10.83□2.28% vs 2.94□0.30%, p=0.0005) and significantly reduced CD11c+ dendritic cells (10.22□1.65% vs 15.17□1.94%, p=0.008).

Conclusion: These data demonstrate that kidney proximal tubule Nrf2-inducible knockout worsened fibrosis and inflammation after severe AKI. These data identify a novel therapeutic target to accelerate repair after AKI and decrease AKI to CKD progression.

ABSTRACT 51

T cell metabolic reprogramming with glutamine antagonist JHU083 after severe acute kidney injury reduces kidney fibrosis/CKD

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Background: Cellular metabolism regulates T cell functions, and metabolic reprogramming by glutamine antagonist pretreatment protected from early injury in acute kidney injury (AKI) J Clin Invest Insight 2023. Severe AKI leads to chronic kidney disease (CKD). Since T cells also mediate organ repair, we studied the effects of glutamine blockade by JHU083 on kidney fibrosis/CKD and immune responses after severe AKI.

Methods: We induced severe (45 minute) unilateral ischemic AKI in B6 wild type mice and administered glutamine antagonist, JHU083, 24h after reperfusion. Kidneys were harvested at 4 weeks and stained with Masson's trichrome. Kidney T cells were analyzed with an immune-metabolic panel using flow cytometry and machine learning tools.

Results: Glutamine blockade by JHU083 reduced kidney fibrosis in the cortex (21.2±4.2 vs 4.0±0.6%, P=0.001) and medulla (17.3±3.2 vs 9.2±1.4%, P=0.038) compared to vehicle. Unbiased high-dimensional analyses segregated T cells from JHU083-treated and vehicle groups. Glutamine blockade markedly increased anti-inflammatory double-negative (DN) T cells (CD4- CD8-), (6.3±0.7 vs 23.4±1.6% of αβT cells, P<.001, 2.2±0.3 vs 3.0±0.2 ×105 cells/g kidney, P=0.035) and naïve CD4 T cells (1.1±0.1 vs 12.8±2.2%, P<.001, 2.2±0.2 vs 6.2±0.7 ×104 cells/g kidney, P<.001), whereas effector-memory CD4 T cells decreased (92.8±0.8 vs 75.9±3.5%, P<.001, 1.8±0.1 vs 0.4±0.1 ×10 cells/g kidney, P<.001). Activation and proliferation were reduced in CD4 (Ki67 94.2±0.5 vs 76.0±3.3%, P<.001; CD69 87.9±0.9 vs 77.2±1.8%, P<.001) and CD8 T cells (Ki67 93.5±0.5 vs 80.8±2.6%, P<.001; CD69 97.5±0.2 vs 94.2±0.6%, P<.001) by JHU083 treatment. JHU083 downregulated hexokinase II (normalized MFI, CD4 0.49±0.04 vs 0.18±0.04, P<.001; CD8 0.42±0.03 vs 0.27±0.04, P=.021), CPT1a (CD4 0.74±0.07 vs 0.13±0.03, P<.001; CD8 0.72±0.08 vs 0.27±0.04, P<.001), VDAC1 (CD4 0.73±0.08 vs 0.13±0.05, P<.001; CD8 0.77±0.07 vs 0.23±0.05, P<.001), and mTOR expression (CD4 0.58±0.04 vs 0.29±0.09 P<.001; CD8 0.29±0.03 vs 0.09±0.02, P<.001), but upregulated Tomm20 (CD4 0.54±0.08 vs 0.32±0.06, P<.001; CD8 0.54±0.08 vs 0.42±0.07, P<.001) in T cells.

Conclusion: T cell metabolism reprograming by glutamine blocker JHU083 administered after severe AKI reduced kidney fibrosis/CKD, increased DN T cells and decreased effector CD4 T cell activation in post-AKI kidneys. This novel approach could mitigate AKI progression to CKD, as well as other causes of CKD progression like diabetes and hypertension.

ABSTRACT 52

Movi: a fast and cache-efficient full-text pangenome index

Mohsen Zakeri, Nathaniel K Brown, Omar Y Ahmed, Travis Gagie, Ben Langmead

Addressing reference bias in genomics is crucial for advancing our understanding of genetic diversity and realizing the full potential of emerging technologies, such as nanopore sequencing. Pangenome indexing plays an important role in overcoming limitations imposed by single-reference genomes, offering a more comprehensive representation of genetic variation. In this context, we introduce Movi, an efficient tool for constructing and querying pangenomes. Movi is designed based on move structure (proposed by Nishimoto and Tabei in 2021) which is the first full text index to achieve constant time query and O(r) space (its size scales with the amount of unique sequence in the reference) simultaneously.

An important advantage of the move structure is strong locality of reference which is exploited by Movi to minimize cache misses. This property makes Movi outpace other full text approaches by tenfold for performing matching queries. Movi's fast query makes it well suited to real-time applications like adaptive sampling for nanopore sequencing, where decisions must be made in a small and predictable time interval.

ABSTRACT 53

Therapeutic Potential of Hyaluronan and Proteoglycan Binding Link Protein 1 for Airway Epithelium in COPD

Bonnie Yeung-Luk, Dheeksha Sudhakar, Brianna Lee, Ethan Tieng, Ethan Sherman, Ethan Gale, Venkataramana Sidhaye

Chronic Obstructive Pulmonary Disease (COPD) caused over 3 million deaths in 2019 and is the third leading cause of death worldwide. COPD is characterized by chronic airway inflammation, progressive airflow limitation, and destruction of lung parenchyma. Remodeling of the airways in COPD involves significant alterations to the extracellular matrix (ECM), affecting airway wall thickness, resistance, and elasticity. Hyaluronan and proteoglycan binding link protein gene family 1 (HAPLN1) is a member of the ECM gene family, playing a critical role in organizing the ECM to maintain the structural integrity of tissues. We aimed to test whether cell treatment with HAPLN1 could improve barrier function in damaged epithelium. We found that HAPLN1 was downregulated in COPD lungs compared to normal lungs. After treating COPD epithelial cells with recombinant HAPLN1 protein, we observed improved barrier function and decreased expressions of genes involved in matrix metalloproteinase (MMP12) and inflammation (IFNA, TGFB1). To examine the impact of fibroblasts on the epithelium, we cocultured fibroblasts with epithelial cells from normal donors. We found that HAPLN1 reduced cigarette smoke-induced MMP12 and TGFB1 gene expression. Additionally, HAPLN1 reduced senescence in the airway epithelium. We induced senescence in the normal lung fibroblast using H2O2 and cocultured them with normal airway epithelium. We found that senescent fibroblasts decreased barrier integrity with downregulation of the cell-cell adhesion gene (CDH1) and upregulation of the airway remodeling gene (SMA). In conclusion, we revealed that HAPLN1 is a critical factor in maintaining healthy airways and lungs, suggesting a novel therapeutic target for incurable COPD.

ABSTRACT 54

Single-Hepatocyte HBV RNA Sequencing Reveals Intrahepatic and Intracellular Viral Diversity In HIV-HBV Co-Infected Individuals

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There are limited data on the liver cccDNA landscape in chronic hepatitis B. We isolated individual hepatocyte equivalents from livers of four HIV/HBV co-infected persons: HB1 was therapy-naïve while HB2, 3, and 6 were taking HBV-active antiretroviral treatment. Total RNA was extracted from each cell, reverse transcribed, then sequenced with HBV-specific primers yielding 1.2 kb HBV pol (1273 to 2521). From tissues with dual peaks in individual cells, intracellular diversity was examined by sequencing multiple aliquots of extracted RNA per cell. Sequences were analyzed using Seqscape.

We estimated an error rate of 1 nucleotide/1.2kb by amplifying and sequencing a single-copy synthetic RNA 15 times; consequently, sequences from single hepatocytes varying from consensus by □3 nucleotides were considered variant. Of 537 cells, 219 (41%) yielded sequences; HB1 86/216 (40%), HB2 21/94 (22%) 18/93 HB3 (19%), and HB6 97/180 (54%). HB2 and HB4 had no variants. In HB1, 40% (34/86) of sequences were variant including 19 sequences with dual peaks and three cells with internal deletions (92 to 277 amino acids). In HB6, who had known drug-resistant HBV, 26% of cells had V173L+L180M+M204V and 27% other cells had dual peaks at these positions. Cells with variants in HB1 and HB6 were spatially non-contiguous. Single-nucleotide polymorphisms (SNPs) were distributed across the amplicon in synthetic RNA, whereas in hepatocytes, SNPs were concentrated in the B domain in HB1 and B and C domains of RT in HB6. Multiple aliquots from 48 additional cell extracts in HB1 and 24 additional cell extracts in HB6 confirmed □□ variant sequences in 24% and 23% of cells, respectively.

Single-cell sequencing demonstrated intrahepatic diversity that was spatially dispersed in 2/4 people suggesting that contiguous cell-to-cell spread has a limited role in disseminating HBV. We found variant sequences within some hepatocytes supporting intracellular diversity generated from a dynamic cccDNA pool.

ABSTRACT 55

Loss of cofilin-1 in the airway epithelium of COPD causes mitochondrial dysfunction

Bonnie Yeung-Luk, Ethan Gale, Austin Niederkofler, Brianna Lee, Samuel Fontaine, Carter Swaby, Baishakhi Ghosh, Venkataramana Sidhaye

COPD is characterized by emphysema and chronic bronchitis. The airway epithelium is the first barrier against lung damage from stimuli. Previously, we reported that barrier dysfunction in patient-derived COPD epithelium is due to cofilin-1 downregulation with increased levels of polymerized actin filaments. Cofilin-1 (CFL1) has also been implicated in mitochondrial function. In this study, we aim to understand the effect of cofilin-1 on mitochondrial function in injured epithelium. Basal cells are the multipotent stem cells of airway epithelium, our data indicate that basal cells from COPD patients exhibited a decrease in mitochondrial membrane potential with induction of mitochondrial DNA copy number as compared to epithelium from normal donors. Consistently, mitochondrial DNA copy number and mitochondrial mass were increased, and mitochondrial respiration and ATP generation were decreased with the reduction in cofilin-1 protein level in differentiated airway epithelium in COPD vs normal. Furthermore, cofilin 1 was knocked down from differentiated normal epithelium using adeno-CFL1 shRNA and overexpressed in normal lung epithelium cell line HBE3KT using lentiviral-CFL1. Downregulation of CFL1 increased mitochondrial mass with increased mitochondrial fission (DRP1) and decreased mitochondrial fusion (MFN1) and mitochondrial biogenesis (SIRT3). Overexpression of CFL1 in HBE3KT increased gene expressions of MFN1 and SIRT3 and increased protein expressions of complex I and IV with the induction of ATP generation. This suggests mitochondrial dysfunction in lung epithelia from COPD patients is at least due to the downregulation of cofilin-1, suggesting targeting cofilin is a potential strategy to improve epithelial health in COPD.

ABSTRACT 56

Digital twins, next era for intraoperative surgical guidance

Hongchao Shu

Digital twins are virtual interactive models of the real world, exhibiting identical behavior and properties. In surgical applications, computational analysis from digital twins can be used, for example, to enhance situational awareness. We present a digital twin framework for skull-base surgeries, named Twin-S, which can be integrated within various imageguided interventions seamlessly. Twin-S combines high-precision optical tracking and real-time simulation. We rely on rigorous calibration routines to ensure that the digital twin representation precisely mimics all real-world processes. Twin-S models and tracks the critical components of skull-base surgery, including the surgical tool, patient anatomy, and surgical camera. Significantly, Twin-S updates and reflects real-world drilling of the anatomical model in frame rate. We extensively evaluate the accuracy of Twin-S, which achieves an average 1.39 mm error during the drilling process. We further illustrate how segmentation masks derived from the continuously updated digital twin can augment the surgical microscope view in a mixed reality setting, where bone requiring ablation is highlighted to provide surgeons additional situational awareness. In conclusion, we present Twin-S, a digital twin environment for skull-base surgery. Twin-S tracks and updates the virtual model in real-time given measurements from modern tracking technologies. Future research on complementing optical tracking with higher-precision vision-based approaches may further increase the accuracy of Twin-S.

ABSTRACT 57

Investigating the effects of HGF and VEGF for improving angiogenesis in Peripheral Arterial Disease: a mechanistic computational model

Rebeca Hannah de M. Oliveira, Brian H. Annex, Aleksander S. Popel

Peripheral arterial disease (PAD) affects more than 250 million people globally and has no cure. Therapeutic interventions have focused on improving blood circulation through pro-angiogenesis therapies, and clinical trials have shown promising results in treating PAD with hepatocyte growth factor (HGF) alone or combined with vascular endothelial growth factor (VEGF). A mechanistic understanding of these growth factors' synergy and distinct effects in a single or combined therapy can help understand and improve their use for stimulating angiogenesis and treating PAD. Computational models provide the flexibility required to investigate, understand, and evaluate the mechanistic effects of this promising therapeutic approach. Here, we present a data-based mechanistic computational model of HGF and VEGF in endothelial cells (ECs) under hypoxia (simulating the PAD environment) to evaluate how HGF and VEGF differently and synergistically affect vascular permeability and EC proliferation, promoting angiogenesis. We design our model based on good modeling practices, including structural and practical identifiability analysis, parameter optimization, and uncertainty quantification. Using global sensitivity analysis on the optimized model, we find the set of parameters in each pathway with a higher influence on determining cell proliferation and vascular permeability. Additionally, we simulate time and dose responses to VEGF and HGF single or combined therapy, predicting their effect on modulating important aspects of angiogenesis. The model we present can be applied to understanding the microvascular events that occur given HGF and VEGF single or combined therapy and can be used to investigate potential interventions to modulate angiogenesis.

ABSTRACT 58

Integrating epigenetic regulation with metabolic signaling in aggressive thyroid cancer

Akshay Sanghi, Tristan Chou, Si Wu, Lihua Jiang, Warren Reynolds, Lisa Orloff, Howard Y. Chang, Joshua J. Gruber, Maya Kasowski, Michael Snyder

Although genetic mutations are causal in human cancers, the contribution of chromatin changes to cancer onset and progression remains less well understood. Multi-omics profiling of human tumors can provide insight into how alterations in chromatin structure are propagated through the pathway of gene expression to result in cancer signaling. We applied multi-omics profiling of 36 human thyroid cancer primary tumors, metastases, and patient-matched normal tissue. Over 80% of the tumors harbored BRAFV600E mutations, and the remaining tumors mostly had activating mutations in the MAPK pathway. Through quantification of chromatin accessibility associated with active transcription units and global protein expression, we identify a local chromatin structure that is highly correlated with coordinated RNA and protein expression. In particular, we identify cancer-specific enhancers located within gene-bodies as predictive of correlated RNA and protein expression, that is independent of overall transcriptional activity. The enhancers are predicted to be activated by MAPK transcription factor binding. These cancer-specific enhancers associated with upregulation of lysosomal peptidase expression in tumors. We show that BRAF inhibition results in loss of lysosomal function in mutants, and perturbation of lysosomal peptidases decreases MAPK activity only in mutant cells compared to wildtype. These analyses suggest that BRAF thyroid tumors integrate MAPK-driven epigenetic regulation with lysosomal signaling in a positive feedback circuit. Using local cancer-specific epigenetic features, we isolated key cancer signaling, making way for potential targets for cancer therapeutics.

ABSTRACT 59

Association of Pre-pregnancy Cardiometabolic Health with Hypertensive Disorders of Pregnancy: Insights from the National Vital Statistics System 2016-2019

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Background: Pre-pregnancy diabetes and obesity are associated with hypertensive disorders of pregnancy (HDP). However, the proportion of cases of HDP in the population explained by these risk factors (population attributable fraction PAF) overall and across racial/ethnic groups is not well characterized.

Methods: We conducted a cross-sectional analysis of data on women with a live singleton birth from the US National Vital Statistics System between 2016-2019. We used logistic regression to estimate the prevalence odds ratio of HDP and included interaction term for race and ethnicity. We calculated the PAF for the effect of diabetes and obesity on HDP, and the predicted probability of HDP across the continuum of pre-pregnancy body mass index (BMI) by race and ethnicity.

Results: Among 13,201,338 women (mean age 29, SD 6 years), 7% had HDP. The prevalence of HDP was highest among American Indian and Alaskan native women(9.1%). Pre-pregnancy diabetes (aOR 2.63, 95%CI: 2.59-2.67) and obesity (aOR 2.95, 95%CI: 2.93-2.97) were associated with HDP. Compared to non-Hispanic White women, the association of diabetes with HDP was strongest among Native Hawaiian and Other Pacific Islanders (NHOPI) (aOR 3.05 95%CI:2.48-3.77) and the association of obesity with HDP was strongest among Asian women (aOR 3.44, 95%CI: 3.35-3.54) (all p for interaction < 0.05). The PAF was highest among NHOPI (obesity 45%, 95%CI: 42%-48%; diabetes 4% , 95%CI: 3.3%-4.1%).

Conclusion: Pre-pregnancy obesity and diabetes are associated with HDP across all racial and ethnic groups. Obesity and diabetes have highest PAF among NHOPI women and should be intensely targeted.

ABSTRACT 60

Uncoupling interferons and the interferon signature explain clinical and transcriptional subsets in SLE

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Background: Systemic lupus erythematosus (SLE) is characterized by increased expression of interferon (IFN)-induced genes, known as the IFN signature, pointing to IFNs as promising therapeutic targets in SLE. However, only a subset of SLE patients who express the IFN signature benefit from type I IFN (IFN-I) targeting in clinical trials, and blocking IFN-II failed to treat SLE, implying distinct endotypes linked to IFNs in SLE.

Methods: To understand mechanisms of disease heterogeneity in SLE, we integrated the analysis of IFN-I, IFN-II and IFN-III activity levels with transcriptional and clinical data from a large prospective SLE cohort. Findings. Clinical and transcriptional endotypes in SLE are distinguished by distinct combinations of IFN families, as well as IFN-independent mechanisms. Specifically, skin involvement was the only manifestation associated with IFN-I alone, whereas systemic features (e.g., nephritis) were linked to co-elevation of IFN-I, IFN-II and IFN-III, implying additive effects of IFNs in severe SLE. For instance, IFN-II was associated with IFN-I-independent transcriptional profiles dysregulated in SLE, including OXPHOS and CD8+GZMH+ cells, and IFN-III enhances IFN-gene expression when co-elevated with IFN-I. Interestingly, in up to 64% of cases, the IFN signature was not explained by IFNs, either individually or collectively. Similarly, manifestations including cytopenias, serositis and anti-phospholipid syndrome were not associated with increased levels of IFNs, indicating IFN-independent endotypes in SLE.

Conclusions: This study provides novel insights into mechanisms of disease heterogeneity in SLE, as well as a rational explanation for the variable response in clinical trials targeting IFNs.

ABSTRACT 61

Increased Sialic Acid Induced by Allergens and Its Potential Regulatory Mechanisms

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Allergen exposure can trigger asthma symptoms in individuals with asthma. Sialic acid is a type of carbohydrate molecule on the surface of cells and plays a role in various biological processes. We sought to investigate whether allergen exposure can induce sialic acid production, and examine the role of sialic acid in allergic airway information and its potential mechanisms. We found that exposure to house dust mite increased a2,6-linked sialic acid levels in large airways and a2,3-linked sialic acid levels in small airways. In contrast, cockroach allergen exposure led to increased a2,6-linked sialic acid in large airways, but no changes were observed in small airways. Interestingly, treatment with the universal Sialyltransferases inhibitor P-3FAX-Neu5Ac led to an improved lung function in a mouse model of asthma. Mechanistically, CD33 (Siglic-3) has been shown to recognize and bind to sialic acid residues. CD33 was found to be highly expressed in the lung tissues of asthmatic mice, especially in lung macrophages. Both microarray and luciferase reporter assays suggested that miR-511-3p, a microRNA associated with macrophage polarization and airway inflammation, may regulate CD33 expression. These findings suggest that allergen-induced sialic acid could contribute to allergic airway inflammation in asthma, with CD33 and miR-511-3p playing pivotal roles.

ABSTRACT 62

PKG phosphorylation of CHIP protects ovariectomized females from myocardial infarction

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Estrogen, recognized as a cardioprotective agent, is associated with heightened protein degradation. However, the precise underlying mechanism and pathway remain incompletely elucidated. The Carboxyl Terminus of Hsc70-Interacting Protein (CHIP) functions as a co-chaperone and ubiquitin ligase. Notably, CHIP has not been linked to protective effects in female mice. Estrogen is also known to augment Protein Kinase G (PKG) activity. Recent findings reveal that PKG plays a crucial role in phosphorylating the C-terminus of Hsc70 at serine 20, facilitating improved binding of CHIP to Hsc70 and thereby enhancing the stability of the CHIP complex. This study employs female CHIP mouse models, specifically those with phosphomimetic (SE) and phosphonull (SA) modifications, subjected to ovariectomy (OVX) and myocardial infarction (MI). Preliminary results indicate that OVX CHIP SE mice demonstrated superior protection against MI, as evidenced by sustained cardiac morphology and function, along with enhanced proteostasis, compared to OVX CHIP SA mice. These findings suggest that phosphorylation of CHIP at serine 20 confers protection to OVX mice following an MI, contributing to heightened proteostasis. In the realm of public health, this project strives to offer critical support to both pre- and post-menopausal women, who face an elevated risk of developing cardiac diseases and potentially progress into heart failure by unraveling the mechanisms through which estrogen causes cardioprotection.

ABSTRACT 63

Upregulated COL18A1/Endostatin Levels Associates with Right Ventricular Fibrosis and Remodeling in Pulmonary Hypertension in Rats

Anjira S. Ambade, Catherine E. Simpson, Paul M. Hassoun, Rachel L. Damico

RATIONALE: Altered fibrosis is an increasingly recognized feature of pulmonary arterial hypertension (PAH). Endostatin (ES) is an angiostatic peptide derived from collagen type XVIII alpha 1 (COL18A1) and is significantly elevated in PAH. Though ES is linked to adverse outcomes and death in PAH, its relationship to fibrosis in disease remains unknown. We hypothesize that increased COL18A1/ES is linked to fibrosis within the right ventricle (RV) during pathologic hypertrophy and remodeling in PH.

METHODS: Male Wistar rats were randomized to Sugen 5416/chronic hypoxia (SuHx) versus vehicle-treated rats housed in room air, and hemodynamics, RV morphology, Masson's trichome staining, tissue hydroxyproline content, and total tissue mRNA were assessed over time. Spearman correlation analysis was performed to examine the relationships between COL18A1 and metrics of RV remodeling, afterload, and fibrosis.

RESULTS: In the SuHx model, COL18A1 abundance in the RV was significantly associated with measures of RV remodeling and afterload, including the ratio of RV weight/body weight (□=0.832, p<0.0001), Fulton's index (☐=0.815, p=0.0001), and RVSP (☐=0.875, p<0.0001). No significant associations were observed between the left ventricle (LV) COL18A1 mRNA levels and measures of RV remodeling and afterload. At 21 days, collagen deposition between RV cardiomyocytes was significantly higher in SuHx vs. control rats (8.9±1.4 vs 0.6±0.1, p<0.0001). The strongest relationships were found between RV COL18A1 mRNA levels and myocardial fibrosis in the RV (☐=0.768, p=0.0005). These morphologic changes were associated with a significant positive association with hydroxyproline content in RV tissue (☐=0.49 μg/mg, p=0.02).

CONCLUSIONS: In the SuHx PH model, the increased COL18A1 expression in the heart was associated with higher pulmonary pressures and pathologic RV remodeling. Furthermore, our results link increased COL18A1 with RV fibrosis and remodeling in the PH setting.

ABSTRACT 64

Cardiovascular Risk Profile Among Reproductive-Aged Women in the United States: The Behavioral Risk Factor Surveillance System (BRFSS, 2015-2020)

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Background: Suboptimal cardiovascular health is associated with adverse pregnancy outcomes and long-term cardiovascular risk. We examined trends in cardiovascular risk factors(RF) and correlates of suboptimal cardiovascular risk profiles among reproductive-aged US women.

Methods: With data from 335,959 women in the Behavioral Risk Factor Surveillance System(2015-2020), we conducted serial cross-sectional analysis among nonpregnant reproductive-aged women(18-44 years) without CVD who self-reported information on eight cardiovascular RF selected based on "Life's Essential 8" metrics. We estimated the prevalence of each RF and suboptimal cardiovascular risk profile(≥2 RF) and examined trends overall, by age and race-ethnicity. Using multivariable Poisson regression, we assessed the sociodemographic correlates of suboptimal cardiovascular risk profile.

Results: The weighted prevalence of women <35 years was approximately 64% in each survey year. The prevalence of suboptimal cardiovascular risk profile increased modestly from 72.4%(71.6%–73.3%) in 2015 to 75.9%(75.0%–76.7%) in 2019(p<0.001). This increase was mainly driven by increases in overweight/obesity(53.1% to 58.4%; p<0.001). Between 2015-2019, significant increases in suboptimal cardiovascular risk profile were observed among non-Hispanic-White(69.8% to 72.6%; p<0.001) and Hispanic(75.1% to 80.3%; p<0.001) but not among non-Hispanic-Black(82.7% to 83.7%; p=0.48) or Asian women(68.1% to 73.2%; p=0.09). Older age, rural residence, non-Hispanic-Black, and Hispanic race-ethnicity were associated with a higher prevalence of suboptimal cardiovascular risk profile.

Conclusions: There has been a modest but significant increase in suboptimal cardiovascular risk profile among US women of reproductive age. Urgent preventive efforts are needed to reverse this trend and improve cardiovascular health, particularly among subgroups at increased risk, to mitigate its implications.

ABSTRACT 65

Dynamic genetic regulation across cellular differentiation in heterogeneous differentiating cultures

Joshua Popp, Katherine Rhodes, Radhika Jangi, Merlin Li, Alexis Battle, Yoav Gilad

Unlocking the potential of personalized genomic medicine requires understanding not only which genetic variants relate to important traits, but how they do so. Pinning down the molecular impacts of genetic variation is notoriously difficult: the vast majority of disease loci act through the regulation of nearby genes, and these regulatory effects play out differently among the myriad cell types, developmental time points, and environmental exposures that occur over the course of a lifespan. Large-scale studies have assayed regulation in only a narrow fraction of the landscape where these variants act, presenting a key bottleneck to the identification of target genes and mechanisms underlying disease loci. In this study, we address this bottleneck by generating heterogeneous differentiation cultures (HDCs) from 53 African-ancestry donors. HDCs are aggregates of induced pluripotent stem cells which spontaneously differentiate into an expansive set of cell types. We performed single-cell RNA-sequencing to over 900,000 cells from this HDC panel, which allowed us to assess the impacts of genetic variation in dozens of understudied, early developmental cell types. We identified thousands of novel regulatory effects, which were enriched at genes involved in diverse processes including circulatory and central nervous system development. We then directly interrogated the regulatory dynamics at play as cells transition between contexts, identifying 18 novel dynamic regulatory effects for variants known to relate to a variety of complex traits. We highlight examples including a musculature-associated variant with a dynamic impact on collagen expression over the course of muscle cell differentiation, and a schizophrenia risk locus with maximal regulatory impact at an early intermediate stage of neuronal differentiation. In summary, HDCs extend the characterization of genetic regulatory effects to an expanded landscape of dynamic cellular environments, with the potential to accelerate the identification of regulatory mechanisms underlying disease risk loci.

ABSTRACT 66

A History of Cervical and Lumbar Pain is a Risk Factor for Constant Abdominal Pain in Patients with Chronic Pancreatitis

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Background: Chronic pancreatitis (CP) pain can be subdivided into two temporal patterns: constant and intermittent. Constant pain has been consistently shown to be associated with lower quality of life more so than the severity of pain. We aimed to identify demographic and clinical characteristics associated with constant pain in chronic pancreatitis.

Methods: The medical records of all adult patients with CP referred to a multidisciplinary pancreatitis clinic between 2010-2022 were evaluated. The presence, severity, and temporality of CP pain was reviewed to classify patients into 3 categories: 1) No pain, 2) Intermittent mild to severe episodes of pain; 3) Constant mild to severe pain. Multivariable logistic regression was conducted to identify variables independently associated with constant pain.

Results: A total of 425 patients were included in the analysis. Of these, 180 (42%) had intermittent pain, and 190 (45%) had constant pain. Older patients (OR=0.1.016 [1.001-1.032], p=.042), presence of psychological disorders (OR=1.548 [0.987-2.426], p=0.05), alcohol etiology (OR=1.684 [1.037-2.736], p=0.035), prescription opioid use on first visit (OR=2.273 [1.451-3.561], p<0.0001), and a history of cervical or lumbar pain (OR=2.198 [1.204-4.011], p=0.01) were associated with constant pain in the adjusted analysis.

Conclusion: A history of cervical or lumbar pain is an independent risk factor for constant pain in CP. This study adds evidence to the concept that prior pain experiences in one region of the body can facilitate the pain of another.

ABSTRACT 67

SPRR2A Contributes to the Recurrent Mechanisms of Chronic Rhinosinusitis with Nasal Polyps through Modulating Nasal epithelial EMT

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Chronic rhinosinusitis with nasal polyps (CRSwNP) is a condition characterized by high tissue heterogeneity. Postoperative recurrence is a common challenge in CRSwNP patients, and our study seeks to elucidate the molecular factors that play a role in the recurrent histopathology of CRSwNP. We conducted RNA-transcriptome sequencing on nasal tissue samples obtained from both CRSwNP patients and healthy individuals. Our analysis revealed a significant up-regulation of several SPRR family members, including SPRR1A, SPRR1B, SPRR2A, and SPRR3, in CRSwNP patients compared to their healthy controls. Of these, the heightened expression of SPRR2A was further confirmed by RT-PCR in an independent cohort of CRSwNP patients. Immunofluorescence staining further highlighted the preferential expression of SPRR2A within the nasal epithelial layer, particularly in cases of recurrent CRSwNP. Notably, we observed similar expression patterns for markers associated with Epithelial-Mesenchymal Transition (EMT), such as α-SMA (alpha-smooth muscle actin) and vimentin. Our in vitro experiments demonstrated that the overexpression of SPRR2A in cultured primary nasal epithelial cells led to an increase in the expression of EMT markers (α-SMA and vimentin) while concurrently inhibiting the expression of epithelial markers, including e-cadherin and ZO-1. In contrast, mice with SPRR2A deficiency displayed decreased expression of α-SMA and vimentin but an increased expression of e-cadherin and ZO-1 in the nasal mucosa of allergen-induced mouse model. Collectively, our study suggests that SPRR2A may contribute to the mechanisms underlying the recurrence of CRSwNP by modulating the process of EMT in nasal epithelial cells.

ABSTRACT 68

Investigating the Current State of Clinical Ethics Training in Hospice and Palliative Medicine Fellowship Programs

Lauren E. Berninger; Danielle J. Doberman

Ethical issues commonly arise in the treatment of seriously ill patients and their families. Studies suggest the majority of clinical ethics consultations involve patients at end of life. As a field that works with seriously ill patients, hospice and palliative medicine (HPM) physicians commonly face ethical challenges. Little has been published on the current state of ethics training in HPM fellowship programs across the United States. We sought to explore the current state of clinical ethics education in hospice and palliative fellowship programs nationwide through a survey-based assessment of HPM fellowship directors in the United States. Additionally, we sought to collect data on the perceived importance of ethics training in HPM fellowships, current methods used to deliver ethics education, potential harms of lack of ethics training and barriers to providing optimal ethics education in HPM fellowship programs. Our preliminary findings revealed 56.3% of HPM fellowship directors rated ethics education as "extremely important" and 31% rated it as "very important". The majority of programs lacked formal ethics training for HPM faculty preceptors and only 46.3% reported having an ethicist or faculty member with advanced ethics training listed as core faculty for their fellowship. A variety of ethical topics were addressed in HPM fellowships through a multitude of different educational modalities. Only 13.2% of programs required a formal rotation in clinical ethics and 50% of programs reported having an elective rotation available. Our findings suggest that more HPM fellowship programs nationwide may benefit from the development of a standardized ethics curriculum.

ABSTRACT 69

Disrupted post-transcriptional regulation of gene expression as a hallmark of severe obesity

Shohei Takaoka, Marcos Emmanuel Jaso-Vera, Xiangbo Ruan

Overnutrition-induced obesity elevates the risk of cardiometabolic diseases and cancer. Understanding the impact of overnutrition on gene expression is crucial for developing strategies to prevent obesity-related ailments. While transcriptional and post-transcriptional mechanisms regulate mRNA levels, their specific alterations during obesity development remain unclear.
Conventional RNA-seq analysis focuses on exon-mapped reads for gene expression, but recent research suggests the reliable use of intron-mapped reads. Our study examined exon and intron levels in liver RNA-seq datasets from mice with seven weeks (short-term) and thirty weeks (long-term) of high-fat diet-induced obesity. At early obesity, the correlation between gene transcription (Δintron) and mature mRNA changes (Δexon) was low, suggesting a broad post-transcriptional regulatory mechanism. This correlation strengthened in severe obesity, indicating a loss of this mechanism. Gene Ontology analysis revealed upregulation of genes related to liver fibrosis and inflammation at early obesity.
To explore post-transcriptional regulation, we identified RNA-binding proteins (RBPs) enriched or depleted in 3' UTR of differentially expressed introns/exons. PTBP1, implicated in mRNA decay, was enriched in the 3' UTR of post-transcriptionally suppressed genes at early obesity. Single-cell RNA-seq showed dramatic downregulation of PTBP1 in hepatocytes and Kupffer cells in severe obesity, suggesting its pivotal role in maintaining post-transcriptional gene regulation. In conclusion, our study highlights the importance of PTBP1-mediated post-transcriptional regulation in preventing undesirable gene expression at the early stage of obesity, a mechanism lost in severe obesity. Restoring hepatic PTBP1 expression may protect against obesity and related diseases.

ABSTRACT 70

Serine Depletion Potentiates Venetoclax Efficacy in Acute Myeloid Leukemia

Alli Abolarin

Acute myeloid leukemia (AML) presents significant challenges, marked by high relapse rates and limited survival despite recent therapeutic advancements. The combination of the BCL-2 inhibitor, venetoclax (VEN), with azacytidine, recently achieved breakthrough approval for elderly AML patients. However, it's therapeutic potential remains hampered as a significant portion of the patient population exhibited no response. This study seeks to enhance the efficacy of VEN by leveraging AML cell metabolism. Specifically, ABT-199 treatment can downregulate key players in the serine synthesis pathway, potentially reducing the flux and limiting the total serine availability in the cell. This renders them acutely sensitive to exogenous serine. Modulating serine levels enhances the efficacy of ABT-199 treatment, and understanding the metabolic rewiring involved carries promise for developing strategies that optimize treatment effectiveness while minimizing dosages.

ABSTRACT 71

In-vivo fundus imaging and autorefraction with a computational lightfield ophthalmoscope

Corey Simmerer, Nicholas Durr

Purpose: Over one billion people worldwide lack refractive eye care and access to screening for retinal diseases. A significant barrier to addressing this problem is the shortage of eye care specialists in low- and middle-income countries. The gap in eye care access is exacerbated by the lack of an affordable, high-throughput, and scalable technology to screen for retinopathies and refractive error. To address these problems, we have developed a computational lightfield ophthalmoscope (CLO) using computational imaging to combine fundus imaging and refraction measurements. This approach enables two measurements through one camera and eliminates the need for moving parts for focusing.

Methods: We modified a Canon CR-DGi fundus camera with a diffuser to capture a computational image of the retina that multiplexes fundus image and wavefront information onto the detector. Deconvolution is used to reconstruct fundus images, and digital refocusing is used to estimate refractive error. A model eye and in-vivo human retinas are used to demonstrate the capabilities of the CLO.

Results: From a single computational image, we reconstruct a fundus image of the eye that can be digitally refocused over a large range of refractive errors in-vivo.

Conclusions: Our device establishes the feasibility of using computational imaging to combine fundus imaging and autorefraction into an optical system that could improve throughput for screening for retinopathies and refractive errors. The CLO has no moving parts, lowering the technical barrier to capturing in-focus fundus images. This device shows promise toward the creation of a portable combination fundus imager and autorefractor.

ABSTRACT 72

Apoptosis Resistance in Pulmonary Arterial Smooth muscle cells (PASMCs)

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We previously demonstrated PASMCs from animal models of pulmonary hypertension (PH) have increased expression of the membrane protein aquaporin 1 (AQP1) and are resistant to apoptosis, the highly regulated pathway terminating in caspase-3 (casp3) activation and cell death. In cancer, AQP1 drives apoptosis resistance; therefore, we hypothesized increased AQP1 contributes to apoptosis resistance in PH PASMCs. PASMCs were isolated from controls or rats injected with vascular endothelial growth factor receptor type 2 inhibitor (Su5416) and exposed to hypoxia (SuHx) to induce PH. In some cells, AQP1 was depleted with small interfering RNA (siAQP1) with a non-targeting control (siNT) or was overexpressed with an adenoviral construct (AdAQP1) with AdGFP as control. Cells were treated with PBS or pro-apoptotic hydrogen peroxide and apoptosis measured by Hoechst staining. Caspase activity was measured via luminescent assay. Depleting AQP1 in SuHx PASMCs restored apoptosis susceptibility while overexpressing AQP1 in control PASMCs reduced susceptibility. At baseline, total casp3 activity was similar in control and SuHx cells, but lower in SuHx nuclear fractions. Stimulated SuHx PASMCs exhibited significantly less total and nuclear casp3 activity. To investigate a potential interaction between AQP1 and casp3, proximity-based biotinylation assays were performed utilizing biotin ligase fusion proteins, which showed a specific interaction between AQP1 and inactive casp3. From these results, we conclude increased AQP1 in SuHx PASMCs interacts with casp3 to prevent activation and/or nuclear translocation, conferring apoptosis resistance. Future studies further characterizing the AQP1/casp3 interaction could provide the basis for novel therapeutic targets focused on restoring PASMC apoptosis susceptibility.

ABSTRACT 73

Fentanyl and xylazine concentrations in urine predict detection times in clinical trial participants

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Aim: Reports suggest persons who use illicit fentanyl test positive in urine longer than established toxicology detection windows, and the excretion profile of xylazine in clinical populations is unknown.

Methods: Participants with fentanyl exposure in a residential study provided up to 4 urine samples daily for 5 days. Quantitative urine concentrations of fentanyl, norfentanyl, and xylazine were determined via a selected reaction monitoring-based liquid chromatography-mass spectrometry assay (lower limit of quantitation [LLOQ] 5 ng/mL). Detection times were calculated from participant's most recent self-reported fentanyl use. Using non-compartmental pharmacokinetic modeling on the spot urine samples, we predicted when each participant's analyte concentrations were expected to reach 5 ng/mL.

Results: Eleven participants provided 3+ urine samples between 05/2022-01/2023. Participants were majority male (82%), of black (55%) or white (45%) race, averaging 42 years old. Most reported intranasal (82%) versus intravenous (18%) fentanyl use. Ten participants (91%) had 1+ urine samples with quantifiable xylazine.
Predictions were included if analyte line R2>0.5 and/or the prediction line confirmed when the analyte reached LLOQ. Fentanyl's average predicted detection time was 74.3 hours (SD=40.2 hours, N=7, 2 confirmed). Norfentanyl's average predicted detection time was 136.0 hours (SD= 64.3 hours, N=4). Xylazine's average predicted detection time was 31.2 hours (SD=16.7 hours, N=7, 3 confirmed).

Conclusion: Since our LLOQ is higher than many qualitative urine drug tests, we predict persons with illicit fentanyl exposure will test positive for >3 days. This is the first study to characterize urinary detection time of xylazine to aid in developing urine toxicology tests.

ABSTRACT 74

Quality of mpox evaluation by clinical site: Infectious disease clinics provide more comprehensive care than other clinical sites

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Introduction: Sexually transmitted infections (STIs) evaluation involves patient interview, clinical examination, and diagnostic testing. Patients with suspected mpox presented to different venues during the 2022 outbreak. Three quality-of-care (QoC) metrics were evaluated.
Methods: Patients tested for mpox in the Johns Hopkins Health System (JHHS) between 06/01/2022 – 12/15/2022 were included. Demographic and clinical characteristics and QoC indicators were extracted. Pearson's chi-squared test compared proportions and logistic regression tested associations.
Results: Of 276 patients tested for mpox, 62.7% (173/276) were evaluated in the emergency department or urgent care setting (EDUC), 18.8% (52/276) in primary care or other ambulatory care (PCAC), and 18.5% (51/276) in sexual health or infectious disease clinic (SHID). Sexual history was documented in 94.1% (48/51) encounters at SHID clinic, 67.3% (35/52) at PCAC and 63.6% (110/176) of EDUC visits. Anogenital exam was documented in 82.4% (42/51), 40.4% (21/52), and 44.5% (77/173) of SHID, of PCAC and of EDUC visits respectively. STI testing was performed in 78.4% (40/51), 38.5% (20/52) and 53.8% (93/173) of SHID, PCAC, and EDUC visits respectively. Differences in each quality measure between venues were statistically significant (p value < 0.001).
A composite outcome combining the three metrics revealed that patients treated in SHID clinic had significantly higher odds ratio of completion compared to care in the EDUC, (OR 4.51 95% CI 2.33-8.73, p value 0.000).
Discussion: Evaluation of patients with suspected mpox differed according to clinical venue. Strategies to improve sexual health assessments include self-reporting of sexual history, self-collection of STI testing specimens and provider training.

ABSTRACT 75

CaMKII hyperactivation in skeletal muscle: a potential driver of sarcopenia?

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Sarcopenia, the loss of muscle size and strength with advanced age, is a major driver of physical frailty and functional decline in older adults. Ca2+/calmodulin-dependent protein kinase II (CaMKII) is an evolutionarily conserved protein with established roles in enhancing skeletal muscle performance and adaptation to exercise training, however excessive CaMKII activity may impair muscle function. To evaluate the potential role of skeletal muscle CaMKII in sarcopenia, we assessed CaMKII activity in young (4 months) and old (20 months) mice and found significantly elevated CaMKII activity in aged muscles. Using an adeno-associated viral vector (AAV9), we expressed a constitutively active CaMKII (CaMKIICA) in the fibers of the tibialis anterior muscle of 3-month-old mice to recapitulate the hyperactivation of CaMKII observed in aged muscles. The CaMKIICA expressing legs displayed a significant loss of force production across a range of stimulation frequencies and a marked reduction of maximal force. Conversely, suppressing CaMKII activity in aged muscles by an AAV9-encoded CaMKII inhibitor (CN19o) showed a trend of beneficial effects for muscle function in old mice. Ongoing studies on intact muscles and single fibers will determine the effects of CaMKII activity on neuromuscular connection, muscle fiber excitability, calcium handling, and functions of myofibrils. Our findings support the role of CaMKII in aging-related loss of muscle function and suggest that suppressing CaMKII activity is a potential intervention against sarcopenia.

ABSTRACT 76

Clara Cell RhoA Promotes Cockroach Allergen-Induced Airway Inflammation through Sprr2a-Mediated Epithelial Barrier Function

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RhoA is known to play a pivotal role in asthma pathogenesis. Our previous research has demonstrated that the specific deletion of RhoA in alveolar type 2 cells exacerbates airway hyperresponsiveness and increases airway inflammation in an asthma mouse model. This study aimed to elucidate the role of RhoA in Clara cells and its contribution to airway inflammation. RhoA-deficient mice in Clara cells were generated by crossing CC10-CreERTM mice with RhoAfl/fl mice (CC10-CreERTM; RhoAfl/fl). We found that deletion of RhoA in Clara cells led to a reduction in allergen-induced airway hyperresponsiveness and inflammation. Multiparameter flow cytometry analysis, encompassing markers for various immune cell types, pinpointed interstitial macrophages (IM) as one of the cell types most affected by RhoA deletion. Moreover, RNA-seq analysis unveiled several top-ranking genes, including Sprr2a, Mcpt1, Tdo2, Ccl24, and IL-13, showing significant down-regulation in the lung tissues of CC10-CreERTM; RhoAfl/fl mice. The reduced expression of Sprr2a was further confirmed through immunofluorescence staining. Importantly, our human study demonstrated that serum levels of Sprr2a were markedly elevated in patients with Th2 high asthma, exhibiting a positive correlation with FeNO (fractional exhaled nitric oxide), induced sputum eosinophils, and serum IgE levels. Mechanistically, Transwell air-liquid interface (ALI) culture experiments employing airway epithelial cells from Sprr2a knockout mice (Sprr2a-/-) showed a decrease in transepithelial/transendothelial electrical resistance (TEER) and an increase in permeability, as evidenced by the penetration of FITC-Dextran. Collectively, our study provides insights into the influence of RhoA in Clara cells on allergic airway inflammation through controlling the Sprr2a-mediated epithelial barrier function.

ABSTRACT 77

Mechanistic Computational Modeling of IL-2 and IL-2 Immunocytokines

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Introduction: Interleukin-2 (IL-2) stimulates the survival, activation, and expansion of T lymphocytes. Due to its critical role in immune function, the IL-2 cytokine has been FDA-approved for the treatment of certain metastatic cancers and used clinically for the treatment of autoimmune conditions such as type 1 diabetes and for the prevention of transplant rejection. However, the off-target effects of IL-2 and its vanishingly short half-life have hampered clinical progress. To circumvent the therapeutic shortcomings of natural cytokines, our lab has tethered IL-2 to anti-IL-2 antibodies to form immunocytokines, which enhance target specificity and significantly prolong serum persistence of IL-2. To advance therapeutic translation, we are building a computational pharmacological model that mechanistically characterizes the activity of IL-2 and IL-2-based immunocytokines.

Materials and Methods: We built and validated a computational mechanistic model of IL-2 and two IL-2 immunocytokines that incorporated ligand-receptor binding, trafficking dynamics, and signaling in two cell types (effector T cells and regulatory T cells). The model included over a dozen molecules, approximately 30 parameters, and close to 40 ordinary differential equations. The model was parameterized using extensive experimental data when available, and physiological estimates when necessary. The level of IL-2 signaling induction (represented in the model as ligand-receptor binding) was used as a predictor of downstream signaling and validated against experimental measurements of signaling induced by IL-2 and IL-2-based immunocytokines.

Results/Discussion/Conclusions: Based on initial model simulations, the relative difference in signal activation between cell types stimulated by IL-2 could be explained by the ligand-receptor binding affinity differences between those cell types; however, affinity disparities could not explain why experimental activity readouts (for both cell types) took place at IL-2 doses well below what would be expected based on ligand-receptor binding affinities alone. Using parameter optimization, we were able to identify binding parameters that could reproduce the experimental data. However, this method was not parsimonious, as it required each combination of ligand and cell type to be independently optimized and therefore did not produce a consistent set of broadly applicable parameters. Instead, we introduced an intermediate signaling step between the ligand-receptor activation and the signaling readout, using a Hill function to permit amplification of the receptor activation. This transformation allowed for the previously-measured binding affinities to reproduce the observed cell-type-specific and ligand-specific responses to IL-2 and IL-2-based immunocytokines using a consistent set of parameters. We are next translating the mechanistic model to a computational pharmacological model to simulate IL-2 and IL-2-based immunocytokines as therapeutics in the body, in order to help accelerate therapeutic regimen development. Further iteration between experimentation and modeling will make the computational mechanistic model more robust and predictive. Better mechanistic understanding of immunocytokines presents a new paradigm for the translation of safe and effective cytokine-based therapeutics, which has the potential to accelerate progress on treatment of conditions such as transplant intolerance, autoimmune diseases, and cancer.

ABSTRACT 78

Deficiency of Nrf2 alters cell differentiation and lung function

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Chronic obstructive pulmonary disorder (COPD) is a chronic inflammatory lung disease that is more susceptible in women. Its pathogenesis is accompanied by epithelial barrier dysfunction and likely subsequent interference in cell differentiation. Epithelial cell differentiation helps repair tissue after damage and targets harmful inhaled substances. Injury to lung epithelium from cigarette smoke exposure leads to oxidative stress and consequential protective activation of master transcription factor NFE2 Like BZIP Transcription Factor 2 (Nrf2) which regulates the expression of antioxidant genes. We seek to investigate the protective role of Nrf2 in mouse airways and lungs. We have revealed that Nrf2 deficiency in female mice exhibited a worsened lung function with increased total lung capacity, compliance and alveolar type 2 cells, and reduced resistance. In the airway, Nrf2 deficiency decreased club cells (marker Scgb1a1, CC10) in both males and females. As basal cells are stem cells of the epithelium and able to differentiate into club cells, we performed Nrf2 knockdown in airway epithelium by treating mouse tracheal epithelial cells (mTECs) derived from Krt5-cre_Nrf2flox/flox with 4-hydroxytamoxifen (4-OHT). Knockdown of Nrf2 in basal cells in female mTECs induced barrier dysfunction, but not in males as well as Nrf2 knockdown in club cells. In summary, the more susceptible and worsened lung function in females than males may be due to the dysregulation of cell differentiation in epithelial basal cells. Further understanding the role of NRF2 in cell differentiation is a potential strategy for maintaining healthy airways and lungs in females.

ABSTRACT 79

Identifying frailty sub-populations based on cell-free DNA tissue of origin

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Circulating cell-free genomic DNA (cf-gDNA) fragments are released into the bloodstream following cell death processes. Higher levels of cf-gDNA are linked to age-related physical and cognitive decline. However, it is unclear which tissues release these fragments, and whether their sources differ in older adults with frailty and cognitive impairment.

Serum cf-gDNA from 190 participants (mean age = 82.3 years; 73% female) in the Religious Orders Study and Rush Memory and Aging Project (ROS-MAP) had DNA methylation performed via Illumina Methylation EPIC array. Next, hierarchical clustering derived distinct patient sub-populations based on cf-gDNA tissue of origin. Linear regression and mixed-effects models examined associations between tissue origin and physical and cognitive measures. Finally, we measured serum metabolomics to identify metabolic changes associated with the sub-populations.

Neutrophils were the most common source (77.7%) of cf-gDNA, followed by vascular endothelial cells (5.3%). Cortical neuron cf-gDNA was detected in 29% of participants. Hierarchical clustering demonstrated three frailty sub-populations distinguished by cf-gDNA tissue origin: cardiovascular, erythrocyte progenitor, and immune cells. Individuals in the cardiovascular sub-population had enrichment of fragments from myocardial and vascular endothelial cells and demonstrated higher frailty scores compared to other sub-populations. Metabolomics analysis demonstrated that individuals in the cardiovascular group had distinct profiles compared to the two other groups for lipid and amino acid metabolism.

This study sheds light on tissue sources for cf-gDNA fragments in community-dwelling older individuals and provides evidence for methods to identify molecular and metabolic pathways that contribute to the heterogeneity observed in frailty.

ABSTRACT 80

Development of a Machine Learning Model for Pulmonary Embolism Prediction in Intensive Care

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Introduction/Background: Pulmonary embolism (PE) is a frequent and life-threatening complication in hospitalized patients. While statistical risk scores have been proposed, there is an unmet need for more accurate methods that can forecast the likelihood for developing PE.

Objective/Problem: Current PE scoring systems (e.g., Modified Wells Scoring System and the Revised Geneva Scoring System) allow clinicians to estimate risk based on a discrete number of predictive factors used as inputs in multivariable logistic regression equations. However, these models have limited predictive accuracy, in part because they may not consider the physiological complexity of acutely ill patients. In this project, we developed and validated a computational model for prediction of PE in critically ill patients.

Methods: Our models were trained on the eICU database, a multi-center intensive-care unit electronic health record dataset that includes demographic and physiological time series data. We externally validated the models on the PMAP database from the Johns Hopkins Hospital. We generated three static models using differing observation windows (12 hours, 24 hours, and 48 hours post-ICU admission) to predict pulmonary embolism any time afterward. Model performance was compared across a variety of different machine learning (ML) algorithms.

Results: The 12-hour logistic regression model displays the largest statistically significant increase in AUROC score compared to current risk scoring systems. Feature importance was explored in each dataset using SHapley Additive exPlanation (SHAP) values.

Our results demonstrate the potential value of ML models using physiological and clinical variables to help predict PE in the ICU.

ABSTRACT 81

AbdomenAtlas-8K: Annotating 8,000 CT Volumes for Multi-Organ Segmentation in Three Weeks

Chongyu Qu, Tiezheng Zhang, Hualin Qiao, Jie Liu, Yucheng Tang, Alan L. Yuille, Zongwei Zhou

Annotating medical images, particularly for organ segmentation, is laborious and time-consuming. For example, annotating an abdominal organ requires an estimated rate of 30–60 minutes per CT volume based on the expertise of an annotator and the size, visibility, and complexity of the organ. Therefore, publicly available datasets for multi-organ segmentation are often limited in data size and organ diversity. This paper proposes an active learning procedure to expedite the annotation process for organ segmentation and creates the largest multi-organ dataset (by far) with the spleen, liver, kidneys, stomach, gallbladder, pancreas, aorta, and IVC annotated in 8,448 CT volumes, equating to 3.2 million slices. The conventional annotation methods would take an experienced annotator up to 1,600 weeks (or roughly 30.8 years) to complete this task. In contrast, our annotation procedure has accomplished this task in three weeks (based on an 8-hour workday, five days a week) while maintaining a similar or even better annotation quality. This achievement is attributed to three unique properties of our method: (1) label bias reduction using multiple pre-trained segmentation models, (2) effective error detection in the model predictions, and (3) attention guidance for annotators to make corrections on the most salient errors. Furthermore, we summarize the taxonomy of common errors made by AI algorithms and annotators. This allows for continuous improvement of AI and annotations, significantly reducing the annotation costs required to create large-scale datasets for a wider variety of medical imaging tasks.

ABSTRACT 82

CFTR Based Therapy for Autosomal Dominant Polycystic Kidney Disease

Cristian Ciobanu, Liudmila Cebotaru

Autosomal dominant polycystic kidney disease (ADPKD) manifests as the formation of fluid-filled renal cysts, ultimately leading to renal failure due to the dysfunction of polycystins (PC) 1 or 2. The RC/RC mouse model, established by Hopp and collaborators, features a R3277C mutation in PC1, resulting in a hypomorphic model with diminished PC1 function. While previous research highlighted the therapeutic potential of CFTR correctors, the pivotal role of CFTR in the reduction of cysts remained questioned. At 30 days of age, a cohort of RC/RC mice was subjected to a single administration of either AAV1 del27-264CFTR or AAV1GFP, followed by sacrifice at the age of 90 days. The treated cohort with del27-264CFTR exhibited a significant reduction in cyst area and size. Both proximal and collecting ducts were effectively targeted by AAV1 GFP, with the del27-264CFTR treatment group demonstrating elevated CFTR levels compared to the control group. Post-treatment, there was a noticeable increase in CFTR colocalization with the basolateral membrane and a decrease in colocalization with the apical membrane. Our results show the pivotal contribution of CFTR to cyst reduction, highlighting the therapeutic potential of AAV1 gene therapy in ADPKD. These findings contribute valuable insights into the potential role of CFTR in mitigating ADPKD progression, shedding light on novel avenues for future research and therapeutic development in this challenging medical condition.

ABSTRACT 83

Dual Treatment with Kynurenine Pathway Inhibitors and NAD+ Precursors Synergistically Extends Lifespan in Drosophila

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Recent research has emphasized the significant impact of the kynurenine pathway (KP) on health and lifespan in humans and mouse models, highlighting the potential of KP manipulation as a therapeutic target. Building on this foundation, our study explores the effects of KP inhibitors and NAD+ precursors on Drosophila lifespan and health. Utilizing DGRP_229 Drosophila, we administered treatments to elevate or suppress KP metabolites, supplement NAD+ levels, or concomitantly suppress the KP while supplementing NAD+ levels. Our findings revealed a notable lifespan reduction in flies with elevated kynurenines. In stark contrast, combination treatments of KP inhibitors and NAD+ precursors significantly enhanced physical functions and extended maximum lifespan. Specifically, in week seven, the combined treatment group exhibited an increase in climbing speed and endurance ($P < 0.0001$) and a substantial decrease in the failure rate during physical performance tests ($P < 0.0001$). Lifespan data showed a 30% increase in average lifespan compared to controls ($P < 0.0001$), surpassing the results of individual treatments. These results underscore the critical role of KP flux in regulating health span and lifespan, suggesting that targeted interventions in KP and NAD+ metabolism can synergistically promote longevity. Our study contributes to the growing body of evidence supporting pharmacological interventions in KP and NAD+ pathways as viable strategies to combat age-related decline in physical function.

ABSTRACT 84

GDF-15 and reduced physical function following total knee replacement: a study of physical resilience and aging

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The metabolic and inflammatory cytokine growth-differentiation factor 15 (GDF15) increases with age and is negatively associated with physical and cognitive function in older adults. We hypothesized GDF15 was also negatively associated with resilient outcomes after surgery. This was tested in the SPRING study of physical resiliency after total knee replacement by assessing the relationship between pre-operative plasma GDF15 levels and postoperative resilience measures including short physical performance battery (SPPB) scores, fatigability, and grip strength. GDF15 analyses and physical resilience measures were assessed in 127 SPRING participants (age 70±6 yrs, n=84 women). Baseline GDF15 levels correlated with age ($r=0.263$, $P<0.05$); age adjusted analyses were applied. In total, pre-operative GDF15 levels did not significantly correlate with functional measures at any timepoint. However, in men (n=43), GDF15 levels correlated with age ($r=0.408$, $P<0.05$) and significant age-adjusted correlations were observed in fatigue ($r=0.368$, $P<0.05$), gait speed ($r=-0.428$, $P<0.05$), and SPPB score ($r=-0.329$, $P<0.05$). Additionally, after age-adjustment GDF15 levels correlated with chair stands at six months ($r=-0.398$, $P<0.05$), SPPB score at six months ($r=-0.384$, $P<0.05$), and gait speed after one year ($r=-0.487$, $P<0.05$). GDF15 did not significantly correlate with changes in SPPB score ($P>0.05$). There were no significant correlations between GDF15 and any of these functional measures in women (r-value range: -0.259 to 0.107; p-value range: 0.112 to 0.969). Elevated pre-operative GDF15 appeared to correlate with worsening physical function following knee replacement in men, but not in women. Further investigation is necessary to understand the relationship between GDF15 and the biology of physical resiliency.

ABSTRACT 85

Structure-Constrained Recoding (SCRecoding) Performs Synonymous Codon Substitution While Preserves Specific RNA Secondary Structures

Jitong Cai, Joel Bader

RNA secondary structures in mRNA protein-coding regions have recently been shown to play important roles in various regulation processes, including RNA stability, start codon selection, translational rates and viral RNA genome replication. However, in the field of RNA engineering, there is a lack of computational tools to preserve particular structures during the process of mRNA codon optimization. Here we introduce SCRecoding (Structure-Constrained Recoding), a synonymous codon substitution method which maintains a given RNA secondary structure. This approach utilizes a pre-labeled indexing strategy to determine potential alternative codons for a given coding sequence based on targeted RNA base-pairings, thereby limiting the search space. In addition, this approach considers not only the similarity between the minimum free energy (MFE) structure of the generated RNA and targeted structure, but also the diversity of the RNA structure ensemble from the predominate structure. We applied this method to Saccharomyces 23S RNA narnavirus genome, which encodes for an RdRp and contains pervasive secondary structures that are crucial for virus replication. Our objective is to recode the RdRp coding sequence while maintaining those essential structural elements. With SCRecoding, we effectively generated a structure-retained, recoded variant of the selected genomic region, and subsequently confirmed virus replication using RT-qPCR. Contrastingly, replication efficiency was diminished in recoded variants that lacked consideration of structural information.

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Association of Guideline Alignment and Medication Concordance with Medication Usage in COPD

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Background: Patients with COPD face multiple barriers to receiving guideline-aligned care, including providers prescribing guideline-misaligned medication regimens and discordance between patients and providers about the medication regimen. However, it remains unclear how guideline misalignment and medication discordance are associated with medication usage.

Methods: This study is a secondary data analysis of the Medication Adherence Research in COPD study (2017-2023). Guideline alignment and medication concordance at baseline were determined as described in prior work. Electronic inhaler monitors were attached to participants' medications for 12 months. Controller adherence was constructed as a binary variable based on an 80% cutoff. Rescue use was defined as number of daily actuations and log transformed. The associations of controller adherence and rescue use with guideline alignment and medication concordance were evaluated using logistic and linear regression, respectively.

Results: Overall, 243 participants were included in this analysis (44% male, 72% White, mean age 68.2 years, mean CAT score 18.0, and mean ppFEV1 56.0%). Average controller adherence was 50.4%, with only 19% of participants adherent ≥80% of the time. Median rescue use was 0.68 actuations/day. Medication concordance was associated with higher controller adherence (aOR 6.4, $p<0.05$). Guideline alignment was associated with lower rescue use as compared to both underuse (β=1.70, $p<0.05$) and overuse (β=0.92, $p<0.05$) categories.

Conclusions: Medication concordance was associated with higher controller adherence, which points to the importance of a strong therapeutic relationship to improving adherence. Guideline alignment was associated with lower rescue use, suggesting that patients on aligned regimens have less need for reliever therapy.

ABSTRACT 87

Concurrent Orthostatic Hypotension and REM Sleep Behavior Disorder are associated with increased motor and non-motor symptoms in early-stage Parkinson's disease

Matthew Meyers, Jeannie-Marie Leoutsakos, Kristi Bigos, Gwenn Smith

Parkinson's disease (PD) is defined by motor symptoms (MS); however, non-motor symptoms (NMS) also make significant contributions to disease progression. Orthostatic Hypotension (OH) and REM Sleep Behavior Disorder (RBD) are NMS associated with a more severe course of illness. The high co-morbidity of OH and RBD has largely been overlooked, limiting understanding of the impact of their co-occurrences in PD. The studies examined the effect of comorbid OH, RBD, or both in early-stage PD.

Participants from the Parkinson's Progression Marker Initiative were grouped based +/-OH and +/-RBD. MS and NMS scores were compared cross-sectionally using non-parametric groupwise comparisons with post-hoc corrections for multiple comparisons. Assessments included Movement Disorder Society-Unified Parkinson's disease Rating Scale (MDS-UPDRS): I-NM aspects of Experiences of Daily Living, II-Motor Aspects of Experiences of Daily Living, III-Motor Exam, and IV-Motor Complications, Montreal Cognitive Assessment (MOCA), MDS-UPDRS I-General NMS, Geriatric Depression Scale Short-form (GDS), State-Trait Anxiety Inventory (STAI), and Autonomic dysfunction: Scale for Outcomes in PD-Autonomic symptoms (SCOPA-AUT).

There were 1253 participants. PD+Both had more severe MS vs PD: MDS-UPDRS II ($z = 6.283349$, $p=4.61e-07$), MDS-UPDRS III ($z = 2.775479$, $p=0.03$), and MDS-UPDRS IV ($z = 3.907059$, $p=8.46e-03$). PD+Both had more severe NPS and autonomic dysfunction vs PD: MDS-UPDRS I ($z= 6.720963$, $p= 9.03e-11$), GDS ($z = 4.038002$, $p= 2.7e-04$), STAI ($z= 4.343689$, $p= 7.01e-05$), and SCOPA-AUT ($z = 7.587936$, $p = 1.95e-13$).

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T cell functional phenotyping on a single cell scale using hydrogel microparticles

Monika Kizerwetter, Doyeon Koo, Dino Di Carlo, Jamie Spangler

Engineered cell therapies, especially chimeric antigen receptor (CAR) T cell therapies, have shown much promise in treating various cancers, most notably hematologic malignancies. However, the success of these therapies is highly variable between cancer types and across patient populations. A growing body of literature suggests that certain T cell functional properties are key drivers of response; thus, it is imperative to develop a more thorough understanding of the functional heterogeneity in T cell populations in order to inform the design of the next generation of cancer immunotherapies. Here, we used a new technology our team developed known as nanovials, which are microfluidically manufactured hydrogel microparticles, to enable the specific activation and capture of secreted products of T cells on a single-cell level. Leveraging this platform, we characterized the secretion of IFN-γ and TNF-α by individual CD8+ T cells harvested from OT-I mice. After initial expansion after isolation, T cells were loaded into functionalized nanovials and specifically activated with OVA peptide. The cells loaded in the nanovials were then separated based on cytokine secretion levels via fluorescence-activated cell sorting (FACS). Unlike traditional cytokine secretion assays which require fixation and permeabilization, cells remain viable throughout our process, allowing for sorted subpopulations to be dissociated from the microparticles, expanded, and further analyzed via cytotoxicity, co-culture, or phenotypic studies. Collectively, our efforts introduce a new paradigm for elucidating the functional properties of immune cells, providing critical insights that will guide the future design of engineered cell therapeutics.

ABSTRACT 89

Optimizing neutralizing antibodies and therapeutic immunization in HIV-1

Jason Chang and Feilim Mac Gabhann

Introduction: The persistence of virus in latent form is a key obstacle to a potential cure for HIV. The latent infection inevitably results in viral rebound after termination of combination anti-retroviral therapy (cART), under which a combination of anti-retroviral drugs is administered. Recent work showed that autologous immunoglobulin G (IgG) antibodies control viral outgrowth in the latent reservoir of HIV to variable degrees in different individuals. The neutralizing ability of these autologous neutralizing antibodies (AnAbs) is due to their recognition of the envelope env protein that buds off the membrane of mature HIV virion. As a result, the HIV env gene is under strong selective pressure; it contains five hypervariable regions that diversify of HIV membrane signature, allow the virus to evade the host adaptive immune response, and create a cycle of co-evolution between the env gene and the AnAbs. This suggests co-administration of anti-retroviral drugs and allogenic antibodies targeting AnAb-resistant variants as a potential approach to achieve long-term HIV remission.

Materials and Methods: Using clinical data from the Multicenter AIDS Cohort Study (MACS) cohort, our lab previously developed and validated a mechanistic model that captures the dynamics of cell-cell and cell-virus interactions during HIV infection. As part of this modeling process, the MACS patients were divided into four subgroups based on the length of time from HIV seroconversion to AIDS diagnosis. Within each of these subgroups we generated a population of 1,000 virtual patients, each with different parameter values defining their HIV model dynamics, but each fitting within the distribution of the clinical training dataset. These virtual populations were subsequently validated against another clinical dataset, and used to simulate potential therapies. Here, we implement the effects of nAbs as a reduction in rate of virus infectivity and do not differentiate between autologous and allogenic nAbs. Within the context of our model, these changes are reflected in the rate of infectivity of CD4+ T cells by HIV, the rate of infectivity of macrophages by HIV, and the rate of infectivity of CD4+ T cells by infected macrophages.

Results and Discussion: Using these virtual-patient mechanistic models of HIV infection, here we study the population variability in the predicted outcome of therapeutic immunization with nAbs. This population model gives an estimate of the overall likelihood of success or failure, and in addition, insight into for which virtual patients is it most likely to work, and which parameters govern the responsiveness to therapy? In our simulations, the timing and longevity of nAb treatment are important determinants of therapeutic success, as measured by low viral load and high T-cell recovery. In addition, we can also vary the strength of nAb activity; at the population level, the fraction of individuals experiencing viral rebound increases with the attenuation of nAb activity. The overall trend appears to be a saturable response that is well described by the Hill equation. However, we found that effects of nAb activity are not permanent; in the case of diminishing nAb activity, viral rebound ultimately follows after the cessation of cART (ATI). In practice, this would mean autologous and allogenic nAbs combined would have to continue to confer specificity to the evolving viral reservoir in order for therapeutic immunization to have a successful outcome. Given the invasiveness of the procedures required to carry out therapeutic immunization, our mechanistic model allows one to simulate complex virtual clinical trials in silico prior to conducting it under clinical settings, with validated virtual patients capturing variability across HIV patient population.

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Mitochondrial CaMKII is a Novel Driver of Cardiometabolic Dysfunction

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Ca2+/calmodulin-dependent protein kinase II (CaMKII) is an established negative regulator of cardiac injury. Both the expression and activity levels of CaMKII are elevated in models of heart failure such as ischemia-reperfusion (I/R) injury and myocardial infarction (MI). This is due in part to CaMKII's role in the regulation of excitation-contraction coupling, apoptosis, activation of hypertrophic programming, arrhythmias and pro-inflammatory signaling. Recently a pool of mitochondrial CaMKII has been identified; there is an observed increase in mitochondrial CaMKII activation with left ventricular dilation following injury in a mouse model of myocardial infarction (MI). This deleterious post-MI phenotype is rescued with genetic mitochondrial CaMKII inhibition; conversely, mice with myocardial and mitochondrial CaMKII overexpression (mtCaMKII) present with severe dilated cardiomyopathy and decreased ATP production. To date, the molecular mechanisms by which mtCaMKII regulates mitochondrial energetics are not fully elucidated. We have identified changes in the activity of enzymes in the mitochondrial electron transport chain and TCA cycle in response to increased CaMKII levels or activity, indicating a novel and critical role in mitochondrial metabolism for this kinase. We are currently mapping the mtCaMKII interactome via liquid chromatography–mass spectrometry (LCMS) and proteomics analysis of both scaffolding interactions with proximity labeling utilizing TurboID technology alongside endogenous protein pulldowns. Additionally, we are identifying novel CaMKII kinase-substrate relationships using an ATP-analogue labeling, in order to identify metabolic enzymes which may be regulated via post-translational modifications by CaMKII. The identification of previously unknown mitochondrial partners for cardiac CaMKII may uncover promising pharmacological targets for cardiovascular therapeutics, as this kinase is a critical player in the progression of HF.

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Prediction of individual unfavorable tuberculosis treatment outcomes in Brazil and India leveraging machine learning

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Background: Unfavorable treatment outcomes of treatment failure, tuberculosis (TB) recurrence, on-treatment loss to follow up, and death frequently occur among patients on treatment for pulmonary TB as does loss to follow-up. Existing analyses of unfavorable treatment outcomes mostly report composite treatment outcomes and use traditional statistical techniques.

Methods: We report the prediction of outcomes from participants enrolled in the Regional Prospective Observational Research for Tuberculosis (RePORT) Brazil and India cohort from 2014-2019. Data was harmonized across different cohorts.

Baseline and longitudinal comorbidities, symptoms, body mass index (BMI), radiology features, and laboratory values were considered as potential predictors. Patients were censored at the time of loss to follow up. Random forest survival models were fit to predict the individual unfavorable outcomes of treatment failure, TB recurrence, and death. Model performance was assessed at landmark intervals and reported as the area under the curve (AUC) of the receiver operating characteristic using 5-fold cross-validation. Relative variable importance was determined by permutation importance.

Results: Among 2,654 patients considered, unfavorable outcomes occurred in 491 (19%) of participants including death (n = 111), treatment failure (n = 186), on-treatment loss to follow up (n=199), and recurrence (n=95). The variables of greatest importance to the death model were hemoglobin, baseline BMI, and HIV status. For the model predicting death, the smoothed average cross-validated AUC at 2 months was 0.87, at 6 months was 0.78, at 12 months was 0.80, and at 24 months was 0.82.

Conclusions: We demonstrated the feasibility of using multinational TB treatment data to create models that predict individual unfavorable treatment outcomes for pulmonary TB. In future work we will create combine these individual models into a joint model to be accessed using a web interface.

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Vericiguat Rescues Cyclic Guanosine Monophosphate Production in Hyperglycemic Human Aortic Vascular Smooth Muscle Cells and Augments Vasorelaxation in Aortic Rings Exposed to Hyperglycemia

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Background: Normal endothelial cell dependent vascular smooth muscle cell function is mediated by nitric oxide (NO), which stimulates soluble guanylyl cyclase (sGC) mediated production of the second messenger, cyclic guanosine monophosphate (cGMP) and results in vascular smooth muscle relaxation. NO bioavailability is impaired in inflammatory stress settings, such as hyperglycemia. We examined whether the sGC stimulator vericiguat, augments cGMP production in human vascular smooth muscle cells (HVSMC) exposed to hyperglycemia and explored its effect on vasorelaxation in isolated aortic rings.

Methods: Aortic HVSMCs were exposed to hyperglycemia (30 mM D-glucose) or normal glucose (control, 4.5 mM D-glucose + 25.5 mM L-glucose) for 24h (n=9 per group). In the treatment group, cells received 1uM vericiguat for 24h. All groups were treated with sildenafil (1uM) and the NO donor, DETA NONOate (0.1uM). After 24h of incubation, cells were lysed and intracellular cGMP was measured by ELISA. Additionally, thoracic aortas were obtained from male c57BL/6 mice (8-12 weeks of age) and exposed to high glucose (HG, 40mM D-glucose) or normal glucose control (NG, 5mM D-glucose + 35mM L-glucose) for 24h. The rings were then placed in an organ chamber bath, pre-contracted with phenylephrine (1uM) and dose response curves to increasing doses of acetylcholine (max 10-5nM) were constructed for three groups: control (normal glucose, HG alone, and HG + vericiguat (1 uM) (n = 8-12 rings per group).

Results: HVSMCs exposed to HG produced significantly less cGMP ([mean + SD]: 1.84 + 0.83 nM) than those exposed to NG (3.4 + 1.66 nM, $p < 0.05$). cGMP production in the presence of HG was rescued when treated with 1uM vericiguat, 3.76 + 1.52 nM ($p<0.05$ vs. HG and $p=0.82$ vs. NG). In isolated mouse aortas, ACh mediated relaxation was impaired following pre-treatment with HG alone (E 10^-6.4 vs 10^-6.99M in the control group, $p < .05$) but was improved when a HG group was also treated with vericiguat (EC 10^-7.6M, $p<0.01$ compared to HG).

Conclusions: The sGC stimulator vericiguat restores cGMP production in the setting of hyperglycemia in aortic HVSMCs. Vericiguat also enhances ACh-mediated vasorelaxation in the setting of hyperglycemia. The findings suggest clinical studies are warranted to investigate the potential of vericiguat as a therapeutic agent to improve vascular endothelial-dependent function which is impaired in hyperglycemia and other pro-inflammatory settings.

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Continuous Glucose Monitor (CGM) Integration into Primary Care Clinics

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Introduction & Objective: Continuous glucose monitoring (CGM) has been historically used by endocrinologists to assess glycemic trends and guide therapeutic changes for people with diabetes. We increased access to this tool by equipping primary care physicians (PCPs) to integrate CGM into their practice via a multidisciplinary team approach.

Methods: 18 PCPs were offered a one-hour video training by endocrinology on CGM interpretation. Referred patients were >18yo with A1c > 8% without past CGM use or an endocrinology visit in the past year. Patients saw a Diabetes Care and Education Specialist (DCES) and/or a pharmacist (PharmD) for diagnostic CGM placement and education on nutrition, medication administration, and physical activity goals. DCES or PharmD reviewed the data with patients and sent recommendations to the PCP. Individuals with data post-intervention for A1c and time in range (TIR) were included.

Results: CGM users (n=41) were [mean (SD)] 62.05 (14.54) years of age and 26.83% female. TIR increased by 29.13% from 42.31% (33.25) at baseline to 71.44% (25.79) at 3 months ($p < 0.001$), due to reduced hyperglycemia (Table 1). The proportion of CGM users meeting the consensus target of TIR ≥70% increased from 21.95% to 58.54% ($p<0.001$). Post-intervention, A1c decreased 2.45 % from 9.62 (1.65) to 7.17 (1.08) ($p<0.001$).

Conclusion: Integration of CGM into primary care clinics is feasible and effective using a multidisciplinary approach.

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Prioritizing drug targets with response functions for biological networks

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Molecular measurements, such as DNA and RNA sequencing, play critical roles in identifying upstream drivers and downstream effectors of disease, and designing therapeutic interventions. However, many proteins cannot be targeted with conventional small molecule drugs and individual effectors may be pathway endpoints with limited influence on other signaling pathways. In contrast, intermediates between driver and effectors may regulate more pathways and be more likely to be druggable. Unfortunately, intermediates are often under-represented in molecular measurements such as differential gene expression analysis. We present NetResponse, a method that ranks intermediates by their ability to perturb signaling from driver to effectors in genome-scale networks. Vertices represent genes and proteins, and edges represent gene regulatory and protein-protein interactions. The NetResponse method is an extension of classic network prioritization methods, graph diffusion and betweenness centrality. Instead of using graph diffusion to rank vertices by proximity to drivers and effectors, NetResponse calculates pathway sensitivities to single-vertex perturbations. Unlike betweenness centrality, which only ranks vertices on shortest pathways, NetResponse ranks all vertices by considering all pathways between driver and effectors. We validated NetResponse with results from assays using 3D organoid models of epithelial cell dissemination. Target rankings predicted by NetResponse correlated stronger with the experimental effect of perturbing the targets to inhibit dissemination than rankings from differential expression, betweenness centrality, and graph diffusion. The results suggest that intermediates capable of interfering with pathways between driver and effectors, but may not be identified by molecular measurements, may be better perturbation candidates than terminal

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AbdomenAtlas: A Large-Scale, Detailed-Annotated, and Multi-Domain Abdominal Dataset for Efficient Transfer Learning and Open Algorithmic Benchmarking

Wenxuan Li, Alan Yuille, Zongwei Zhou

We introduce the largest annotated CT dataset (termed AbdomenAtlas) of 22,532 three-dimensional CT volumes sourced from 94 hospitals across diverse populations, geographies, and facilities. AbdomenAtlas provides 684,752 high-quality masks of anatomical structures in the abdomen annotated by a team of expert radiologists with the assistance of AI algorithms. We have radiologists manually annotate 22 anatomical structures in the first 5,000 CT volumes. Following this, a semi-automatic annotation procedure is performed for the remaining, where radiologists revise the annotations predicted by AI, and in turn, AI improves its predictions by learning from revised annotations. Such a large-scale, detailed-annotated, and multi-domain dataset is needed for two reasons. Firstly, it can serve as an important resource for developing AI algorithms at scale, branded as large pre-trained models, which alleviate the annotation workload of expert radiologists to enable broader clinical AI applications. We create a suite of large pre-trained models, showing superior transfer learning ability than preexisting public models. Secondly, it can establish a widely adopted benchmark for evaluating AI algorithms—the more data we use to test algorithms, the better we can guarantee reliable performance in complex real-world scenarios (e.g., clinical settings). Jointly hosted by ISBI & MICCAI conferences, an international competition named Body Maps: 3D Atlas of Human Body is launched using our AbdomenAtlas dataset, aiming to develop and benchmark advanced AI algorithms. We hope our AbdomenAtlas dataset can set the stage for larger-scale clinical trials and offer exceptional opportunities to practitioners in the medical imaging community.

ABSTRACT 96

A Deep Learning Approach to Compute Intracranial Pressure from Extracranial Physiologic Waveforms Routinely Recorded in the Intensive Care Unit

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Abstract: Intracranial pressure (ICP) is a physiological measure used in treating patients with serious brain dis- orders such as traumatic brain injury and stroke. Existing methods to measure ICP are invasive and incur appreciable risks. We hypothesized that ICP can be computed noninvasively from extracranial physiological signals routinely acquired in the Intensive Care Unit (ICU): arterial blood pressure (ABP), photoplethysmography (PPG), and electrocardiography (ECG). We analyzed 600 hours of high frequency (125 Hz) ICP, ABP, ECG, and PPG waveform data simultaneously acquired in 10 patients admitted to the ICU with critical brain disorders. The waveforms were segmented in non-overlapping 10-second windows and ABP, ECG, and PPG were used to train deep learning (DL) models to predict concurrent ICP. The predictive performance of six different DL models was evaluated in single- and multi-patient iterations. Ablation analysis was conducted to evaluate and compare model contributions from single physiologic sources. The mean average error (MAE) ±SD of the best performing models was 1.34 ± 0.59 mmHg in the single- patient and 5.10 ± 0.11 mmHg in the multi-patient analysis.

Ablation demonstrated performances which were statistically indistinguishable between physiological sources for these top DL models (MAE±SD 6.33 ± 0.73, 6.65 ± 0.96, and 7.30 ± 1.28 mmHg, respectively, for ECG, PPG, and ABP; p= 0.42). Results support feasibility and preliminary accuracy of DL-enabled continuous noninvasive ICP computation using extracranial physiological waveforms. With validation, this method could represent an alternative to invasive ICP, enabling real-time assessment and timely treatment of patients with critical brain injuries.

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CD36 regulates Factor VIII secretion from liver endothelial cells

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Abnormal levels of the coagulation factor VIII (FVIII) are a risk factor for venous thromboembolism (VTE). Genome-wide association studies have identified novel candidate gene associations that may regulate FVIII levels in humans, including CD36. We hypothesized that CD36 regulates FVIII release from endothelial cells. We identified a subset of human liver endothelial cells (HLEC) expressing FVIII and purified them using a differentially expressed cell surface protein CD32. CD32+ HLEC expressed FVIII, transported FVIII in intracellular vesicles, and secreted FVIII. We stimulated CD36 signaling or silenced CD36 to test the effect of CD36 on FVIII release. Oxidized LDL (oxLDL), a CD36 agonist, increased endothelial release of FVIII. Conversely, silencing CD36 decreased FVIII release. We searched for an intracellular signaling pathway that mediates CD36 stimulation of FVIII secretion and found that oxLDL increased p38 activity and a p38 inhibitor decreased FVIII release. Taken together, our data show that CD36 stimulates FVIII release through a p38 dependent pathway in specialized liver endothelial cells. These results validate genetic epidemiology data linking CD36 to FVIII levels in humans and provide new insights into the regulation of FVIII levels. This new pathway offers

ABSTRACT 98

Teaching the History of Eugenics to Stimulate Curiosity and Reflection about the Role of Physicians in Society

Shatika Bhat, Mark Hughes

Background: The goal of eugenics is to enhance the genetic quality of human beings. Medicine's role in the dark history of eugenics holds many lessons for current and future physicians. Only 16% of North American medical schools have a required curriculum on the history of medicine in the Holocaust. A Mid-Atlantic medical school offers a selective based on the United States Holocaust Memorial Museum exhibit "Deadly Medicine: Creating the Master Race." After the first session tracing the evolution of eugenics in Nazi Germany, students share their reflections on discussion board postings (DBP). To gain insight on the implications of this history for students' development as physicians, we conducted a qualitative analysis of 12 years' worth of available DBP.

Methods: The eugenics selective is offered to 15-20 first year medical students. After the first session led by a historian, students write about their impressions of the role of physicians in society, people with disabilities, and the implications of eugenics history for contemporary medicine.

For this study, DBP were de-identified. NVivo software was used for qualitative analysis. After developing the initial codebook, 2 investigators double coded all DBP, refined the codebook, and reached consensus on coding definitions and coding. A mind map was developed to show the relationship between major codes. Themes were abstracted, and a conceptual framework was created to show the interactions between themes. Representative DBP quotes were selected.

The institutional review board (IRB) determined the study to be exempt from IRB review.

Results: Of the 221 course participants, 199 DBP (90%) were available for analysis. Coding generated 17codes. 2 main themes and 5 subthemes emerged:

1) Impact of Newfound Knowledge on Learners (elicits both negative and positive emotions; stimulates curiosity about eugenics history and its application to contemporary medicine);

2) Guidance for Physicians (attention to societal forces that shape expectations and behaviors of physicians; remembering the humanity of patients; physician responsibility to avoid the same wrongs).

Conclusions: Teaching the history of eugenics fosters a desire to reflect on the role of physicians, cultivates compassion for patients, stimulates ethical discourse, and enriches the meaning of professionalism. Medical schools and practicing physicians would benefit from exploring the history of eugenics.

ABSTRACT 99

Label Free Microfluidic Purification Strategy of Retinal Ganglion Cells

Takayuki Suzuki, Cynthia Berlinicke, Donald J. Zack, Soojung Claire Hur

In the realm of regenerative medicine, advancements in stem cell biology have led to various treatment strategies for lost body function such as vision loss in Glaucoma and age-related macular degeneration (AMD). In such treatment strategies, the effective purification of the stem cells used in treatment is a critical step for successful regeneration of lost function. Furthermore, a label free technique or an antibody-, cell modification- free purification technique is ideal to avoid unwanted cell response and to meet Federal Drug Administration (FDA) regulations. In this study, we develop a microfluidic based label free technique to purify human stem cell derived Retinal Ganglion cells (RGC) to be used for treatment of Glaucoma and AMD. We suspend purified RGC and non RGC (nRGC) in Phosphate Buffered Saline (PBS) solution supplemented with a FDA approved, non-cytotoxic polymer and inject them into a rectangular microfluidic device. The presence of polymer in the suspension solution induces viscoelastic hydrodynamic forces on RGC and nRGC, making them behave differently in flow causing the cells to concentrate at different positions across channel cross-section. By adjusting flow conditions and device design, we maximize the difference in position between RGC and nRGC cells, thus guiding them to separate outlets for purification. This study exemplifies the potential of microfluidic label-free methods for advancing stem cell based therapeutic approaches.

ABSTRACT 100

Impact of Lumbar Laminectomy & Laminotomy on Spinal Biomechanics: A Systematic Review

Mary H. Foltz, Alexandra H. Seidenstein, Andrew H. Kim, Gabriel Nazario-Ferrer, Craig Almeida, Amit Jain, Jill Middendorf

Lumbar spinal stenosis is a common diagnosis associated with low back pain. For chronic low back pain, a surgical decompression procedure may be indicated, with two of the most common techniques being either a laminectomy or laminotomy. A laminectomy entails removing one or more laminae, while a laminotomy removes only a portion of the lamina. The advantage of a laminotomy is that there is less bone removal than a laminectomy; however, there is a greater risk of inadequate nerve root decompression. Conversely, laminectomies have an increased risk of pars interarticularis (PI) fracture, hence requiring additional surgeries. In silico models may elucidate the success of spinal decompression surgery by informing the altered spinal biomechanics - including the range of motion (ROM), intervertebral disc pressure, and PI stress. Hence, this systematic review aimed to examine existing finite element models and compare the biomechanical outcomes of spinal decompression interventions.

Twenty-one studies were reviewed for our research, which included laminectomies, hemilaminectomies, unilateral laminotomies, bilateral laminotomies, and facetectomies. With an increase in bone removal, there was an increase in the ROM and intervertebral disc pressure. In contrast, the stress at the PI was rarely studied and inconsistent at best.

Therefore, laminectomies may contribute to instability, intervertebral disc degeneration, or annular fissures. While laminotomies may provide more stability and decrease the chance of intervertebral disc degeneration and annular fissures. More research is needed to uncover the PI stress and understand the risk factors associated with the incidence of PI fracture. Understanding the spinal biomechanics of various spinal decompression surgeries allows patient-specific surgical plans based on underlying patient needs and pathologies, optimizing functional outcomes.

ABSTRACT 101

Multi-Dimensional Laser Induced Microfluidic Valve System Based Combinational Antibiotics Susceptibility Screening and Sub-5 Minute Pathogen Identification

Lai Wei, Fangchi Shao, Sixuan Li, Sayuni Dharmasena, Arman Mirmiran, Kuangwen Hsieh, Jeff Tza-Huei Wang

Overusing broad-spectrum antibiotics, due to the slow process of traditional bulk bacteria identification and antibiotic susceptibility testing (ID & AST), has raised severe public health concerns regarding antibiotic resistance. Despite innovations such as PCR and FISH, these methods still face challenges, such as a high risk of contamination and suboptimal accuracy, which hamper their effectiveness in clinical settings. In response, we herein report the Multi-Dimensional Laser-Induced Microfluidic Valve System as a promising solution for rapid and accurate bacteria ID and AST. The system combines a microfluidic valve-based automated combinational multi-sample assembling platform, a multi-channel laser-induced fluorescent single-cell resolution optical detection system, an innovative thermal permeation-based assay hybridizing fluorescent oligonucleotide probes and 16S ribosomal RNA, and a multi-dimensional Quadratic Discriminant-based machine learning bacteria ID algorithm. This unique combination allows our system to achieve automated bacteria identification with 98% accuracy among 7 different bacteria species in under 5 minutes and high-throughput combinational AST in under 1 hour with high specificity and sensitivity. Taken together, the Multi-Dimensional Laser-Induced Microfluidic Valve System represents a rapid, simple, specific, sensitive, and versatile solution for bacteria detection and antibiotic susceptibility testing, and portends an important role in the fight against antibiotic resistance.

ABSTRACT 102

From Fiery Furnace to Bone Fixer: Unveiling the Processing-Structure-Property Relationships in Magnesium Alloys for Enhanced Biodegradable Implant Design

Sreenivas Raguraman, Maitreyee Sharma Priyadharshini, Tram Nguyen, Ryan McGovern, Andrew Kim, Adam Griebel, Paulette Clancy, Timothy Weihs

Magnesium alloys present a compelling alternative to conventional orthopedic implant materials due to their biodegradability, biocompatibility, and impressive mechanical characteristics. However, their rapid deterioration in vivo poses a challenge to practical applications, jeopardizing their mechanical integrity. This study delves into the evolution of mechanical and degradation properties when the alloys are first subjected to elevated temperatures. Utilizing efficient characterization techniques such as X-ray diffraction and microscopy, we swiftly assessed microstructural changes post-thermal treatment. The results revealed the influential roles of grain boundary and strain hardening in enhancing hardness, while factors such as texture, dislocation density, and precipitates impacted corrosion. We conduct a Pearson correlation coefficient analysis to unravel the relationship between the individual microstructural properties and the targets, namely hardness and corrosion. We also employ feature selection machine learning methods, including XGBoost and LASSO, to identify the dominant microstructural factor among these closely correlated variables. This thorough investigation offers valuable insights into the intricate relationships between processing, structure, and properties in magnesium alloys, thereby paving the way for the development of superior biodegradable implant materials.

ABSTRACT 103

Bioengineered platforms to identify links between chronological age and T cell motility and morphology

Yoseph W. Dance, Zhuoxu Ge, Chanhong Min, Annaka Saffron, Charles Ezenwanne, Nicholas Milcik, Nicolas Macaluso, Pratik Kamat, Kendall Pyndell, Jeremy D. Walston, Sean X. Sun, Jude M. Phillip

In this work, we have engineered a variety of in vitro screening platforms to quantify the "fitness" of T cells obtained from human patients that span a wide range of chronological ages. These platforms are constructed using native ECM proteins (e.g., collagen) and using microfluidic devices, which serve as physical obstacles for T cells as they navigate their local microenvironment. High-throughput computational analyses are applied to quantify T cell motility and morphology at single-cell resolution, and we assess how these biophysical features change as a function of age.

ABSTRACT 104

In vivo sickle cell blood rheology in humans

Marisa M. Morakis, Luojie Huang, Gregory N. McKay, Nicholas J. Durr

Sickle cell disease (SCD) is a Mendelian genetic disorder caused by a mutation in the β-hemoglobin gene, resulting in sickle hemoglobin, HbS. HbS polymerizes into long, inflexible chains when blood is deoxygenated, producing stiff and brittle red blood cells. Sickled cells hemolyze and adhere to endothelial walls, causing vaso-occlusion events, chronic inflammation, vasculopathy, and organ damage, among other complications. Although discovered in 1910, there are few treatments available for people with SCD, and the disease mechanisms are not fully understood. Microfluidic and mouse models are often used to study adhesion and occlusion mechanisms of SCD and to test treatment efficacy, but these do not accurately reflect an in vivo human environment. We have recently developed a microscope capable of visualizing ventral tongue capillary blood flow in vivo in humans at a high resolution using oblique back illumination microscopy. Using an IRB-approved protocol, we imaged healthy volunteers and patients with sickle cell disease at the Sickle Cell Center for Adults before and after their simple transfusions to visualize changes in biomarkers such as occlusion events, rheology, and adhered cells. Sickle cell patients demonstrated improved flow speed, fewer occlusion events, and fewer adhered cells after transfusion, while healthy volunteers provided a benchmark for biomarker comparison. We also recorded vaso-occlusive events initiated by sickle RBC adhesion rather than WBC adhesion as was previously theorized. This research enables in vivo study of human sickle cell blood flow, which can be used to assess outcomes and guide development of treatments and therapies for SCD.

ABSTRACT 105

Self-Supervised Learning of Whole and Component-Based Semantic Representations for Person Re-Identification

Siyuan Huang, Yifan Zhou, Ram Prabhakar, Rama Chellappa, Chun Pong Lau

Interactive Segmentation Models (ISMs) like the Segment Anything Model have significantly improved various computer vision tasks, yet their application to Person Reidentification (ReID) remains limited. On the other hand, existing semantic pre-training models for ReID often have limitations like predefined parsing ranges or coarse semantics. Additionally, ReID and Clothes-Changing ReID (CCReID) are usually treated separately due to their different domains. This paper investigates whether utilizing precise human-centric semantic representation can boost the ReID performance and improve the generalization among various ReID tasks. We propose SemReID, a self-supervised ReID model that leverages ISMs for adaptive part-based semantic extraction, contributing to the improvement of ReID performance. SemReID additionally refines its semantic representation through techniques such as image masking and KoLeo regularization. Evaluation across three types of ReID datasets – standard ReID, CC-ReID, and unconstrained ReID – demonstrates superior performance compared to state-of-the-art methods. In addition, recognizing the scarcity of large person datasets with fine-grained semantics, we introduce the novel LUPerson-Part dataset to assist ReID methods in acquiring the fine-grained part semantics for robust performance.

ABSTRACT 106

Understanding the impact of Thermo-mechanical Processing on the Mechanical Properties and Corrosive Behavior of Biodegradable Magnesium Alloys

Andrew Kim, Sreenivas Raguraman, Karthik Muthukkumar

Magnesium alloys have increasingly gained recognition as orthopedic implant materials due to their impressive mechanical properties, biocompatibility, and biodegradability. These properties surpass those exhibited by traditional permanent implants because they minimize stress shielding and eliminate the need for subsequent removal. However, magnesium alloys face challenges due to their rapid deterioration, downgrading their beneficial mechanical abilities. This study addresses this issue by observing the effect of thermo-mechanical processing, specifically cold rolling and annealing, on the high strength ZXM100 and ZX10 alloys. The study utilizes Vickers microhardness, micro-tensile analysis, and fractography to assess their mechanical behavior pre and post processing. Microstructural properties are also observed by implementing characterization methods such as X-ray diffraction, optical microscopy, and SEM. The results reveal that cold rolling induces significant grain refinement which greatly improves the microhardness due to strain hardening. However, faster corrosion rates are also identified likely due to texture and dislocation density. We seek to better understand the impact on mechanical properties by studying tensile strength, obtained through performing micro-tensile procedures. Such efforts will help us understand the relationship between thermo-mechanical processing and mechanical properties, further accelerating the development for superior biodegradable implants.

ABSTRACT 107

Deciphering molecular signatures of epithelial cell state for the progression of cystogenesis in ADPKD using single-cell analysis

Hyun Jun Jung, Patricia Outeda, Owen M. Woodward, Terry Watnick, Paul A. Welling

Autosomal Dominant Polycystic Kidney Disease (ADPKD), caused by genetic mutations in Pkd1 or Pkd2 genes, is the most common form of polycystic kidney disease characterized by the development of cysts in the kidneys. Its progression varies among individuals. In mouse models, the induction of Polycystin gene knockout before or after postnatal day 13 (P13) affects cyst growth rates, leading to the development of early-onset or late-onset ADPKD. However, the epithelial cellular transition around P13 is poorly understood.

To identify transcriptomic changes associated with cell state transition, single nucleus RNA sequencing (snRNA-Seq) was performed on whole kidneys obtained from mice with an intact Pkd gene (Pkd2fl/fl; Pax8-rtTA; TetO-Cre-). Kidney tissues were obtained at P13 (n=2) and P15 (n=2), and 54,324 nuclei (50,000 read pairs per nucleus) were analyzed. snRNA-Seq successfully identified cell populations according to known kidney cell types, including the proximal tubule, loop of Henle, distal tubule, and collecting duct. Importantly, proliferative epithelial cells were identified from different tubule origins. Differential gene expression analysis (P13 vs P15) in proliferative epithelial cells revealed 1,639 differentially expressed genes, with 6 genes (Dapk2, Exoc3l2, Gli2, Slc14a2, Greb1, A330015K06Rik) consistently changed across cell types. Among these genes, 316 genes were mapped on the curated gene set of secretory proteins. Furthermore, 48 genes, including growth factors and known cystogenic factors, changed selectively in each cell type were identified.

In conclusion, this study provides a resource of potential bioindicators for the cell state transition of proliferative epithelial cells associated with the progression of cystogenesis in ADPKD.

ABSTRACT 108

Unrolled IPPG: Video Heart Rate Esitmation via Unrolling Proximal Gradient Descent

Shenoy, Vineet; Marks, Tim K.; Mansour, Hassan; Lohit, Suhas

Imaging photoplethysmography (iPPG) is the process of estimating a person's heart rate from video. In this work, we propose Un- rolled iPPG, in which we integrate iterative optimization updates with deep learning-based signal priors to estimate the pulse wave- form and heart rate from facial videos. We model the signal extracted from video as the sum of an underlying pulse signal and noise, but instead of explicitly imposing a handcrafted prior (e.g., sparsity in the frequency domain) on the signal, we learn priors on the signal and noise using neural networks. We solve for the underlying pulse sig- nal by unrolling proximal gradient descent; the algorithm alternates between gradient descent steps and application of learned denoisers, which replace handcrafted priors and their proximal operators. Using this method, we achieve state-of-the-art heart rate estimation on the challenging MMSE-HR dataset.

ABSTRACT 109

A sustained release antifibrotic prevents stricture formation in preclinical models of Crohn's and other GI tract strictures

Ling Li, Rachel L Shapiro, Henry T. Hsueh, Aditya Josyula, Steven N. Steinway, Kevan J. Salimian, Laura M. Ensign, Florin M. Selaru

Background & aims: Fibrosis in the GI tract represents a leading cause of morbidity and mortality. In Crohn's disease, more than one third of patients will experience stricture formation. Treatment options include medical therapy to target inflammation, endoscopic dilation as well as surgery. However, the treatment outcome is suboptimal. Currently, there are no effective therapies to specifically target the fibrosis process at the site of strictures. In this study, we aimed to develop a stricture therapeutic that (1) has high intrinsic anti-fibrotic properties, (2) can be delivered in a sustained fashion so that it can be (3) delivered topically at the time of endoscopic stricture dilation. We hypothesized that a sustained release antifibrotic has the potential of modulating healing processes, maintaining the lumen diameter, with the net result of decreased further endoscopic or surgical interventions.

Methods: A high-throughput drug screening was performed to identify small molecules with antifibrotic properties. We found that sulconazole has high intrinsic anti-fibrotic properties. Next, sulconazole was formulated as sustained released nanocrystals. Two rodent fibrosis models and a swine model of GI strictures were utilized to verify the therapeutic effect.

Results: We demonstrate that the sustained release nanocrystal formulation of sulconazole (Sul-NC) is effective at reducing fibrosis in two relevant mouse fibrosis models. Most importantly, in a patient-like swine model of GI tract strictures, a single injection of Sul-NC after balloon dilation prevented re-stricturing.

Conclusions: Sul-NC is an effective anti-fibrotic in preclinical models of GI tract strictures. Further studies are needed for clinical translation.

ABSTRACT 110

The impact of a course on the history of eugenics on trainee professional identity formation

Michael Eamonn McCarthy, Mark Thomas Hughes

Background: Trainee formation has long been a goal of medical education, with recent literature calling for an increased emphasis on professional identity formation (PIF). PIF is defined as the transformation of a lay person into a physician, focusing on humanistic domains including professionalism, ethics, and interpersonal skills. Additionally, teaching the history of eugenics has received growing attention, culminating in the recent Lancet report on medicine, Nazism, and the Holocaust. This study investigates learner reactions to a course on the history of Nazi eugenics offered at Johns Hopkins University School of Medicine.

Methods: Student online discussion board posts (DBP) from 2011 to 2022 were exported from web-based learning management systems, de-identified, and uploaded to NVivo, a collaborative qualitative analysis software. DBP were independently coded by two investigators via an inductive approach. Seventeen codes were identified, twelve of which were selected for thematic analysis as content relevant to physician ethical behavior.

Results: Of the 221 course participants, 199 DBP (90%) were available for analysis. Eight themes highlighted the lessons identified by students relating to PIF: universal ethics, conscience, dangers of scientism, public health and individual care, utilitarianism, ambiguity, rational intentions, and the influence of authority.

Conclusions: These findings indicate that student engagement with the history of eugenics advances PIF by fostering reflection on bioethics, the role of physicians in society, and patient care. Students identified universal principles and individual conscience as core guides which, informed by humanistic patient-centered care and a tolerance for ambiguity, aid in future ethical decision making.

ABSTRACT 111

Large Duct Chronic Pancreatitis and Exocrine Insufficiency Predict Increased Fibrosis in Patients undergoing Total Pancreatectomy with Islet Autotransplantation (TPIAT)

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Background: The risk factors for pancreatic fibrosis across the mechanistic stages of CP are not known. The aim of this study was to evaluate the demographic, clinical and radiologic factors for their association with fibrosis in patients undergoing total pancreatectomy with islet autotransplantation (TPIAT).

Methods: All patients undergoing TPIAT for recurrent acute (RAP) and chronic pancreatitis (CP) between 2011-2023 were evaluated for this study. RAP and CP were defined as per the revised Atlanta classification, with at least 2 imaging documented episodes of acute pancreatitis (AP) and the M-ANNHEIM criteria, respectively. Large duct CP was defined as pancreatic duct obstruction due to a stricture and/or stone using cross-sectional imaging. Patients who underwent completion pancreatectomy (n=2) and who only had frozen sections (n=2) were excluded. Excisional biopsies of the pancreatic head (proximal) and body/tail (distal) region were obtained at the time of TPIAT. The Fibrosis Score (FS) was used for histologic assessment which categorizes fibrosis as focal/diffuse and perilobular/intralobular with scores of 1-6, with 6 being the most severe. Total FS was defined as the average perilobular and intralobular FS from excisional biopsies of proximal and distal regions. Exocrine pancreatic insufficiency (EPI) was defined by presence of clinical symptoms and/or fecal elastase-1 <200 mcg/g which improved with use of pancreatic enzyme replacement therapy. Multiple linear regression analysis was used to evaluate the effects of age, BMI, genetic etiology, disease duration (from the time of 1st symptoms or episode of AP to the TPIAT), large duct disease, EPI, and the use of anti-diabetic medications on the FS. These specific variables were chosen a priori based on evidence from the medical literature. Variance inflation factor (VIF) assessments were conducted to examine potential multicollinearity among independent variables, ensuring the reliability of the regression estimates.

Results: There were 88 patients evaluated for this study with a mean age 38±14 years and 46 (52.3%) were female. A total of 37 and 54 patients underwent TPIAT for RAP and CP, respectively. Genetic (52.3%) and idiopathic (37.5%) were the most common etiologies for pancreatitis. The mean FS was 6.52±3.53 with a mean perilobular fibrosis score of 3.71±1.85 and mean intralobular fibrosis score of 2.8±1.90. Large duct CP ($\beta = 2.24$, $p = 0.009$) and EPI ($\beta = 2.64$, $p = 0.002$) were significant predictors of increased FS after adjusting for age, etiology, disease duration and use of diabetes medications. In the analysis of collinearity using VIF, the results indicated no significant collinearity among the variables.

Conclusion: Large duct CP and EPI are independent predictors of increased fibrosis among patients undergoing TPIAT. The role of endoscopic or surgical decompressive therapies to prevent or forestall the development of EPI among large duct CP patients requires further study.

ABSTRACT 112

Promoting Embedded Research in a Learning Health System (PERLHS)

Jodi Segal, MD, MPH and Jill Marsteller, PhD

Promoting Embedded Research in a Learning Health System (PERLHS)
Jodi Segal, MD, MPH Division of General Internal Medicine and
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Bloomberg School of Public Health
Background: Johns Hopkins Medicine is a signatory to the Core Values Underlying a National-Scale Person-Centered Continuous Learning Health System (LHS); our leaders recognize that the LHS model is central to the care of patients. To support this goal of continuous learning, we were awarded funding to become a specialized center to train embedded researchers in learning health system methodologies.

Methods: We are one of 16 centers to receive funding from the Agency for Healthcare Research and Quality to launch PERLHS (Promoting Embedded Research in a Learning Health System). This five-year award allow us to offer an 11-month program, five times, during which a cohort of PERLHS scholars will complete asynchronous didactic learning, participate in monthly workshops, access patient and system data, and complete a mentored project to fulfill a need of their sponsoring entity. We will prepare these embedded investigators to apply rigorous methods to generate and disseminate knowledge and implement changes across the Johns Hopkins Health System. We are engaging three populations of embedded researchers for training.
Results: Presently we are developing the curriculum and processes of the PERLHS Academy. The curriculum builds upon comparative effectiveness and implementation science expertise of Johns Hopkins faculty. We are recruiting our first cohort of embedded learners: a) learners embedded in the Johns Hopkins InHealth Precision Medicine Centers of Excellence; b) learners with operational roles in Johns Hopkins Medicine; and c) learners embedded in the entities advancing patient and population health across Maryland, including Federally Qualified Health Centers. We are also recruiting one post-doctoral trainee, who will work collaboratively across the projects of several scholars, while developing skills.

Conclusion: We will complete the curriculum development and recruitment in the next four months and begin the training in July 2024. The PERLHS scholars will conduct mentored, embedded research supported by core and needs-based didactic training, as well as core and needs-based experiential learning. We will evaluate the PERLHS Academy's impact on embedded scholars, and the impact of the scholars' work on their entities' goals, looking toward sustainability of PERLHS after the completion of the award.

ABSTRACT 113

High Dimensional Consensus spectra for Single-Compound Forensic Drug Discrimination

Rowy(Wencheng) Zhong; Anthony Kearsley

Mass spectrometry is commonly used for identification and classification of chemical compounds. The output from a mass spectrometer is typically characterized by a display of mass-to-charge ratios (m/z) of ions as a function of their intensities. Within these profiles, distinct peak patterns are studied, such as the highest or Base Peak, molecular ion peaks and isotopic peaks.

Particularly, in our method, we focus on the top k highest peaks and offer a mathematical description of how similar two compounds are in a probabilistic manner. We employed what we call, High Dimensional Consensus spectra (HDC), a novel method utilizing probabilistic peak statistics, by assuming the availability of replicated data for the compounds. Preliminary results suggested that HDC leverages measurement variability to improve sensitivity of similarity measures between similar compounds, such as Fentanyl and Fentanyl analogs - compounds with similar mass spectra signal.
Identifying compounds given only mass spectral profiles is a common practice in fields like drug design and discovery, screening of metabolites, and clinical practice. In this poster we will focus on a different application, the identification of illegal drugs, such as Cocaine and Heroin, listed in the Federal Control Substances Act. In particular, we highlight the resilience of HDC by showcasing its performance against various types of noise in samples. This emphasis on robustness is of significant interest to law enforcement, aiming to enhance the identification of illegal drug compounds, especially those collected in less-than-ideal circumstances.

ABSTRACT 114

Differential Stroke Volume Between Left and Right Ventricles As Predictor of Clinical Outcomes: The MESA Study

Ashkan Abdollahi, Yoko Kato, Hooman Bakhshi, Vinithra Varadarajan, Omar Chehab, Ralph Zeitoun, Mohammad R. Ostovaneh, Colin O. Wu, Alain Bertoni, Sanjiv J. Shah, Bharath Ambale-Venkatesh, David A. Bluemke, João A. C. Lima

Background: Valvular heart diseases and intra-cardiac shunts associated with congenital heart disease can cause persistent disruption in the balance between left (LV) and right (RV) ventricular stroke volumes (SV). However, the prognostic value of such imbalances has not been established among asymptomatic individuals in a general population.

Methods: 4,058 participants from multi-ethnic study of atherosclerosis who had a cardiac MRI at cohort inception were included in this study. ΔSV was calculated as LVSV-RVSV, and participants were classified as: Balanced ΔSV: -30 mL ≤ ΔSV ≤ 30 mL; Negative ΔSV: ΔSV < -30 mL; Positive ΔSV: ΔSV > 30 mL. Multivariable Cox proportional hazard regression models were applied to compute hazard ratios for the association between ΔSV and mortality, heart failure (HF), and atrial fibrillation (AF).

Results: The average age of the participants was 61±10 years, with women making up 52% of the cohort. Participants were followed during a median follow-up period of 17 years (IQR, 16.9-17.1) for AF and 18.4 years (IQR, 18.3-18.5) for other outcomes. At baseline 1.2% of participants (n=47) had ΔSV > 30 mL, 2% (n=80) had ΔSV < -30 mL, and 96.8% (n=3931) had ΔSV between -30 and 30 mL. During follow up 1,006 participants died, 235 developed HF, and 764 developed AF. After adjusting for demographics and baseline cardiovascular risk factors, ΔSV > 30 mL was associated with increased mortality (HR 1.73; 95% CI 1.12-2.67; p=0.01), HF (HR 2.40; 95% CI 1.11-5.20; p=0.02), and AF (HR 1.89; 95% CI 1.16-3.08; p=0.01). These relationships were independent of LV and RV function at baseline. ΔSV < -30 mL solely linked to HF (HR 2.09, 95%CI 1.09-3.99; p=0.02) and lost significance after adjusting for baseline LV function.

Conclusions: In a multi-ethnic cohort of participants free of cardiovascular disease at baseline, LVSV exceeding RVSV by at least 30 mL was independently associated with lower long-term survival and greater risk of HF and AF.

ABSTRACT 115

HMGA1 modulates transcriptional networks involved in plasticity in KMT2A-r acute myeloid leukemia

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The High Mobility Group A1 (HMGA1) chromatin regulator gene is overexpressed in refractory acute myeloid leukemia (AML) and diverse solid tumors, although mechanisms underlying HMGA1 are only beginning to emerge. KMT2A-r acute myeloid leukemia (AML) is a highly lethal form of AML caused by rearrangements of the KMT2A gene (KMT2A-r), which encode fusion proteins that induce pro-leukemogenic genes (HOXA). We therefore sought to examine HMGA1 in KMT2A-r AML. We hypothesized that: 1) HMGA1 drives plasticity in KMT2A-r AML by altering chromatin state and transcriptional networks, and, 2) Targeting HMGA1 will enhance sensitivity to therapy. In two KMT2A-r AML patient cohorts, HMGA1 is highly overexpressed. Further, HMGA1 levels increase in KMT2A-r AML cells that become resistant to cytarabine (AraC), suggesting that HMGA1 endows AML cells with the capacity to survive and expand after AraC. To examine HMGA1 function in KMT2A-r AML, we silenced HMGA1 expression in KMT2A-r cell lines by CRISPR or short hairpin RNA approaches. Strikingly, HMGA1 deficiency disrupts leukemogenic properties, including proliferation and clonogenicity in vitro and leukemic engraftment and expansion in immunosuppressed mice transplanted with KMT2A-r AML cells. Accordingly, survival was also increased in recipients of AML cells with HMGA1 silencing. Targeted gene expression studies reveal that HMGA1 induces HOXA genes in KMT2A-r cell lines. HMGA1 also occupies the HOXA9 promoter region by chromatin immunoprecipitation. To define additional mechanisms underlying HMGA1 in KMT2A-r AML, multi-omics studies are underway. Together, these findings implicate HMGA1 as a novel epigenetic regulator of HOX genes and promising therapeutic target in KMT2A-r AML.

ABSTRACT 116

Measurement practices and clinical management of Lipoprotein(a) levels at Johns Hopkins Hospital from 2017 to 2021: A retrospective study

Yehuda Eidensohn, Anjali Bhatla, Jie Ding, Seth S. Martin, Francoise A. Marvel

Background: Elevated lipoprotein(a) [Lp(a)] is an independent, genetically determined risk factor for atherosclerotic cardiovascular disease (ASCVD). We evaluated the frequency of screening for elevated Lp(a) and subsequent management at a large academic institution over a 5-year period.

Methods: The Johns Hopkins Hospital (JHH) electronic medical record was queried to identify patients with an encounter between 2017-2021, either with established ASCVD or at high risk, defined as being on any lipid lowering medication or having LDL ≥ 190 mg/dL. The frequency of Lp(a) testing and of elevated levels (≥75 nmol/L) were identified for each year.

Results: Among 111,350 unique adult patients, 2,785 (2.5%) had at least one Lp(a) test. Patients with Lp(a) testing, compared to those without testing, were younger (mean age 56 years vs. 66) more likely to be female (49% vs. 44%) and non-white (46% vs. 34%) and had higher LDL (median 118 vs. 91 mg/dL; p<0.001) The number and frequency of Lp(a) testing increased from 167 (0.57%) in 2017 to 1155 (5.67%) in 2021. Lp(a) levels were elevated in 43.4% of patients (moderate [75-125]: 10.3%, high [125-600]: 32.2%, severe [>600]: 0.9%). Among 920 patients with high or severe Lp(a) levels, 200 (22%) had a subsequent referral to cardiology or lipid specialist, and 180 (20%) had a subsequent lipid-lowering medication prescribed.

Conclusion: At our healthcare institution, the frequency of incident Lp(a) testing among high-risk patients was low but increased over the study period.

ABSTRACT 117

Surgical risk prediction using an explainable deep learning approach applied to pre-operative 12-lead electrocardiograms

Carl Harris, Anway Pimpalkar, Ataes Aggarwal, Xiaojian Chen, Patrick Yang, Wanting Shan, Joseph Greenstein, Casey Overby Taylor, Robert Stevens

Surgical decision-making is critically dependent on an accurate assessment of risk. Despite routine use of electrocardiography (ECG) in the clinical setting, the value of this test in surgical risk stratification is not well understood. Using 12-lead diagnostic ECG taken prior to major noncardiac surgery in 36,299 adult patients enrolled in the MIMIC-IV dataset, we trained a series of convolutional neural network-based models to predict major post-surgical adverse outcomes including acute myocardial infarction (MI), in-hospital mortality (IHM), and a composite of MI, 30-day mortality, and stroke. These waveform-only models achieved comparable discrimination to the Revised Cardiac Risk Index (RCRI), a benchmark pre-surgical risk stratification tool used to evaluate non-cardiac surgical candidates. We then integrated ECG waveforms with a small number of clinical variables (age, sex, and RCRI components) to create a fusion model. The fusion model achieved an AUROC of 0.818 (95% CI [0.795, 0.839]), 0.828 (95% CI [0.809, 0.847]), and 0.758 (95% CI [0.748, 0.768]) for MI, IHM, and composite outcomes, significantly outperforming models based on ECG waveforms (MI: p=0.044, IHM: p=1.46□10^-8, composite: p=3.14□10^-29) or RCRI alone (MI: p=0.002; IHM: p=4.33□10^-11; composite: p=2.25□10^-19). To gain insight on the explainability of the models, we generate counterfactual ECGs using generative adversarial networks. Given an input ECG, our explainability module produces a set of plausible modifications to the waveform that allows us to visualize morphological differences relevant to the outcome classification verdict. We then show that these counterfactual ECGs provide credible explanations for classifier decisions.

ABSTRACT 118

Cell type specific CaMKII activation patterns revealed by CaMKAR, a bioactivity reporter deployable in living cells

Alex Severino, Oscar E Reyes Gaido, Bian Liu, Erick O Hernandez-Ochoa, Richard L Huganir, Elizabeth Luczak

The multifunctional Ca2+ and calmodulin-dependent protein kinase II (CaMKII) dynamically couples intracellular Ca2+ to fundamental cellular responses, and excessive CaMKII activity contributes to cellular dysfunction in excitable cells. Despite the importance of CaMKII in health and disease, basic measurements of CaMKII activity are lacking in living cells due to the lack of adequate biosensors. We recently developed the CaMKII Activity Reporter (CaMKAR), a tool that allows for a real-time, reversible, fluorescence-based readout of CaMKII activation. We expressed CaMKAR in three types of excitable cells (cardiac myocytes, skeletal myofibers and neurons) in order to measure the temporal dynamics of CaMKII activation. In neonatal rat cardiac myocytes, CaMKAR signal reached peak intensity within 60 seconds following stimulation with angiotensin II or electrical field pacing. In primary mouse skeletal myofibers, it took 1 hour to achieve statistically significant increase in CaMKII activity following field stimulation. Finally, in rat hippocampal neurons, CaMKAR signal that reached peak intensity within 1.5 seconds following stimulation with glycine. Taken together, these signal measurements across cardiac and extracardiac tissues demonstrate, for the first time, that CaMKII operates over a broad range of temporal dynamics in different cell types. CaMKAR will allow us to conduct future experiments aimed at identifying the drivers behind the diversity in CaMKII kinetics to further our understanding of this fundamental molecular signal important for human pathophysiology.

ABSTRACT 119

Using dynamic network analysis to improve the diagnostic reliability of scalp EEG for epilepsy

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Epilepsy is a disorder characterized by recurrent seizures that affects 3.4 million people in the United States. The misdiagnosis rate of epilepsy is around 30%. One standard, but underutilized, diagnostic test is scalp EEG. When analyzing the EEG, clinicians visually inspect for events called interictal epileptiform discharges (IEDS). However, these events are only detectable in 29-55% of recordings. An always-present EEG marker would greatly improve the test's reliability in the diagnosis of epilepsy.

We performed a retrospective study of 198 subjects seen at four epilepsy centers. All patients were initially diagnosed with epilepsy, but after long-term monitoring 107 patients' epilepsy diagnosis were confirmed, and 91 diagnoses were overturned for psychogenic non-epileptic attacks. The scalp EEG records were collected, all of which were void of IEDs and therefore provided no diagnostic utility with traditional methods.

From the scalp EEG, we calculated a series of dynamic network metrics, namely by analyzing the fragility and the sources and sinks of the network. These features were used to train a logistic regression model which output the probability that each patient had epilepsy. The model's receiver operating characteristic curve had an area under the curve of 0.94. Using a probability threshold of 0.61, the model achieves an accuracy of 0.904, sensitivity of 0.835, and specificity of 0.963.

Instead of detecting specific events, network analysis allows us to find inherent properties of an epileptic brain. The use of this tool could greatly improve the reliability of scalp EEG in the diagnosis of epilepsy.

ABSTRACT 120

Multi-organ mapping of age-related changes to the female mouse reproductive system at cellular resolution

Yutong Zhu, Mia Grahn, Winni Zheng, Aanya Kheterpal, Ashleigh Crawford, Gretchen Alicea, Yu Shen, Andre Forjaz, Nick Milcik, Jeremy Walston, Denis Wirtz, Ashley Kiemen

Advanced maternal age is associated with infertility and a heightened risk of adverse health complications, particularly post-menopause. The reduction in muscle content leads to laxity in the vaginal wall, cervical, and uterine muscles. Furthermore, the cumulative effect of scarring and inflammation heightens the risk of various reproductive organ abnormalities, including ovarian cysts, uterine fibroids, fallopian tube blockage, and increases the likelihood of gynecological cancers. While existing efforts have predominantly focused on individual organ abnormalities, there is a need for comprehensive quantitative mapping of the reproductive system as a whole. Here, we explore the relationship between age-related abnormalities of the female mouse reproductive system using a quantitative tissue mapping approach.

We employed CODA, a deep-learning-based technique to reconstruct microanatomy at subcellular resolution from serially sectioned hematoxylin and eosin (H&E)-stained tissue to map the entire female reproductive system of eight mice. The reproductive systems were serially cut into an average of 868 serial sections per mouse and reconstructed using a nonlinear image registration algorithm. Deep learning semantic segmentation was used to quantitatively label 22 tissue structures, including normal and abnormal structures of the gynecological system, with an overall accuracy of 92.4%. Our findings revealed that, post-menopause, the total volume of reproductive organs increases, predominantly driven by abnormal structures such as ovarian and uterine cysts, which are often found in proximity to one another. This research has the potential to increase our understanding of the multi-organ changes undergone by the human reproductive system with age.

ABSTRACT 121

Correcting for Rater Effects in Operating Room Surgical Skills Assessment

Ryan Chou, Hajira Naz, Kofi D. O. Boahene, Jessica H. Maxwell, John R. Wanamaker, Patrick J. Byrne, Ira D. Papel, Theda C. Kontis, Gregory D. Hager, Lisa E. Ishii, Sonya Malekzadeh, S. Swaroop Vedula, Masaru Ishii

Surgical skills assessments are used for the training, certifying, credentialing, and privileging surgeons, the establishment of national benchmarks and surgical curricula, and machine learning methods. Rater effects cause inter-rater variation in these assessments and can obscure the true skill of trainees.

In our study, 7 attending surgeons (raters) rated 41 residents and fellows (trainees) who performed 188 nasal septoplasties using seven items from the Septoplasty Global Assessment Tool. To model a rater effect adjusted latent surgical skill, we fit a structural equation model with the item scores regressed on a latent component of skill that included the rating surgeon as a random effect. We validated the model against conventional measures of skill including the level of expertise and post graduation year (PGY) commensurate with the trainee's performance, the trainee's actual PGY, and whether the surgical goals were achieved.

The magnitude of the rater coefficients (i.e. the impact of the rater effect) was almost as high as the skill coefficients for some items. Adjusted scores increased with attending-estimated skill levels and PGY of trainees, increased with the actual PGY, and appeared constant over different levels of achievement of surgical goals.

We propose a method to adjust surgical skill assessments, from the operating room using structured rating scales, for rater effects. This method can be applied to national-level databases, allowing for the creation of standardized (i.e., adjusted for rater effects) quantitative surgical skill benchmarks.

ABSTRACT 122

Enhanced Medical Visualization in Augmented Reality

Xinrui Zou

Augmented Reality (AR) is reshaping user environments by integrating digital content with the real world. Despite its potential, AR's adoption in healthcare is limited by perceptual challenges, particularly depth misestimation in Optical See-Through Head-Mounted Displays (OST-HMDs). Addressing this is crucial for accurate medical visualization inside the patient's body. My research is developing AI-driven visualization techniques in AR to enhance digital content perception, aiming to enrich medical practices by providing surgeons with additional information, seamlessly integrated into their workflows. The core research question is whether we can surpass the perceptual limitations of OST-HMDs to deliver consistent, accurate depth cues for in-situ medical imaging. The hypothesis is that advanced visualization techniques will improve depth perception, thus increasing medical procedure accuracy and effectiveness. The AR system under development integrates volumetric rendering with advanced methods like photorealistic rendering and AI-assisted anatomical coloring, deepening the understanding of medical volumes. Preliminary findings have led to an AR framework that effectively manipulates and visually distinguishes various anatomies, offering surgeons a comprehensive view of complex structures. This progress supports my early career goal as a first-year Ph.D. student: to bridge the gap between cutting-edge AR technology and clinical application, contributing to medical AR's practicality in enhancing patient care. The potential of this research to be applied in real medical scenarios aligns with my ambition to become a medical AR specialist, aiming to make AR an essential tool in clinical settings.

ABSTRACT 123

One model to segment multiple sclerosis lesions with high accuracy, generalization, and versatility: multi-center validation of single-center trained models

Jinwei Zhang, Lianrui Zuo, Blake E. Dewey, Samuel W. Remedios, Yihao Liu, Savannah Hays, Dzung L. Pham, Aaron Carass, and Jerry L. Prince

Automatic multiple sclerosis (MS) lesion segmentation using multi-contrast magnetic resonance (MR) images provides improved efficiency and reproducibility compared to manual delineation. Current state-of-the-art automatic MS lesion segmentation methods utilize modified U-Net-like architectures. However, in the literature, dedicated architecture modifications were always required to maximize their performance. In addition, the best-performing methods have not proven to be generalizable and versatile to diverse clinical test datasets with contrast variations, missing contrasts, and image artifacts. In this work, we developed an accurate and generalizable MS lesion segmentation model using the well-known U-Net architecture without further modification. A novel test-time self-ensembled lesion fusion strategy is proposed that not only achieved the best performance using the ISBI 2015 MS segmentation challenge data but also demonstrated robustness across various self-ensemble parameter choices. Moreover, equipped with instance normalization and contrast dropout training strategy, the model trained on the ISBI challenge data generalized well on clinical test datasets from different scanners.

ABSTRACT 124

Prescribing of Evidence-based Medications for the Prevention of Adverse Cardiovascular Events and Progression of Chronic Kidney Disease Among Patients with Diabetes

Samantha Pitts, Lisa Yanek, Justin Wu, Alisa Mayas, Erin Michos, Nes Mathioudakis, Nisa Maruthur

Background: Atherosclerotic cardiovascular disease (ASCVD) is the leading cause of mortality in the US. Among patients with diabetes and established or high risk of ASCVD, there is strong evidence for reduction of cardiovascular outcomes, including cardiovascular and all-cause mortality, with the use of glucagon-like peptide-1 receptor agonists (GLP1 RA) and sodium-glucose transport protein-2 inhibitors (SGLT2i). SGLT2i have also demonstrated benefits in patients with heart failure (HF) and chronic kidney disease (CKD).1 As a result, the ADA recommends GLP1 RA and/or SGLT2i use as first line agents independent of the need for glycemic control in populations with ASCVD, HF, and CKD.2 The proportion of patients with type 2 diabetes in primary care at Hopkins receiving GLP1 RA and SGLT2i is unknown.

The overarching aim of this study is to understand gaps in the prescribing of GLP1 RA and SGLT2i among patients with diabetes in primary care at Johns Hopkins to inform an intervention to improve their utilization and reduce cardiovascular outcomes among these high-risk patients.

Methods: We identified patients with at least one visit to a Johns Hopkins primary care location in the prior 12 months with type 2 diabetes, determined by at least one visit diagnosis for type 2 diabetes (E11 – E14). We further classified patients with diabetes as having an indication for a GLP1 RA or SGLT2i if they had at least one visit diagnosis for ASCVD (I20 - 25), CKD (N18) or HF (I50). We defined patients as having been prescribed a GLP1 RA or SGLT2i if they had at least one medication order identified.

Results: Among 183,203 patients with a visit in primary care in the prior 12 months, 26,560 (14.5%) had type 2 diabetes, of whom 11,722 (44.1%) had one of the three co-morbid conditions, indicating high risk for major cardiovascular adverse events. ASCVD was most common [7862 (29.6% of all patients with diabetes)], followed by CKD [6508 (24.5%)], and HF [3862 (14.5%)]. Among patients with diabetes and one of the three co-morbid conditions, 5885 (50.2%) had ever received a GLP1 RA or an SGLT2i.

Conclusion: Only half of patients with diabetes in seen in primary care at Hopkins in the past 12 months have any medication order for evidence-based medications for the prevention of major adverse cardiovascular events and progression of chronic kidney disease. Additional study is necessary to refine the definitions of the target populations (e.g., CKD with estimated glomerular filtration rate <60 or proteinuria), examine current use of these medications, and to understand barriers to prescribing to guide the development of interventions to improve the use of SGLT2i and GLP1 RA among high-risk populations with diabetes.

ABSTRACT 125

One model to segment multiple sclerosis lesions with high accuracy, generalization, and versatility: multi-center validation of single-center trained models

Jinwei Zhang, Lianrui Zuo, Blake E. Dewey, Samuel W. Remedios, Yihao Liu, Savannah Hays, Dzung L. Pham, Aaron Carass, and Jerry L. Prince

Automatic multiple sclerosis (MS) lesion segmentation using multi-contrast magnetic resonance (MR) images provides improved efficiency and reproducibility compared to manual delineation. Current state-of-the-art automatic MS lesion segmentation methods utilize modified U-Net-like architectures. However, in the literature, dedicated architecture modifications were always required to maximize their performance. In addition, the best-performing methods have not proven to be generalizable and versatile to diverse clinical test datasets with contrast variations, missing contrasts, and image artifacts. In this work, we developed an accurate and generalizable MS lesion segmentation model using the well-known U-Net architecture without further modification. A novel test-time self-ensembled lesion fusion strategy is proposed that not only achieved the best performance using the ISBI 2015 MS segmentation challenge data but also demonstrated robustness across various self-ensemble parameter choices. Moreover, equipped with instance normalization and contrast dropout training strategy, the model trained on the ISBI challenge data generalized well on clinical test datasets from different scanners.

ABSTRACT 126

Gene count normalization in single-cell imaging-based spatially resolved transcriptomics

Lyla Atta, Kalen Clifton, Manjari Anant, Jean Fan

Recent advances in imaging-based spatially resolved transcriptomics (im-SRT) technologies now enable high-throughput profiling of targeted genes and their locations in fixed tissues. Normalization of gene expression data is often needed to account for technical factors that may confound underlying biological signals. Here, we investigate the potential impact of different gene count normalization methods with different targeted gene panels in the analysis and interpretation of im-SRT data. Using different simulated gene panels that overrepresent genes expressed in specific tissue anatomical regions or cell types, we find that normalization methods that use scaling factors derived from gene counts differentially impact normalized gene expression magnitudes in a region- or cell type-specific manner. We show that these normalization-induced effects may reduce the reliability of downstream differential gene expression and fold change analysis, introducing false positive and false negative results when compared to results obtained from gene panels that are more representative of the gene expression of the tissue's component cell types. These effects are not observed without normalization or when scaling factors are not derived from gene counts, such as with cell volume normalization. Overall, we caution that the choice of normalization method and gene panel may impact the biological interpretation of the im-SRT data.

ABSTRACT 127

ArthroNeRF: Advancing Intraoperative Scene Reconstruction and View Enhancement in Arthroscopic Surgeries Using Neural Radiance Fields

Zheyuan Zhang

The ArthroNeRF project aims at significantly advancing arthroscopic surgery, a minimally invasive technique that requires high dexterity and spatial awareness from surgeons. This project utilizes Neural Radiance Fields (NeRFs), a neural network architecture, to enable intraoperative scene reconstruction and enhance the surgical field of view. Its main objective is to simplify the mental process of understanding complex anatomical structures during arthroscopic procedures.

We hypothesize that providing alternative views from the perspective of surgical instruments can assist surgeons during task performance. To achieve this, we developed a framework that uses an arthroscopic camera to capture detailed images of the patient's anatomy. These images train a NeRF to reconstruct the scene, creating a virtual model of the patient's anatomy. This virtual model, used in combination with the position of surgical instruments, renders synthetic viewpoints of the patient's anatomy in real time, complementing the arthroscopic camera's feed. This additional perspective provides surgeons with valuable information to better understand the anatomy and tool placement.

The project has yielded promising results in enhancing surgical viewpoints. A user study with 18 participants demonstrated its potential to reduce task completion time and facilitate the learning process for tool manipulation. ArthroNeRF effectively combines advanced computational imaging with medical applications, marking an innovative contribution to the field of minimally invasive surgery. This technology promises not only to improve surgical performance but has also shown the potential to decrease the learning curve for these complex procedures.

ABSTRACT 128

Enhancing Surgical Precision and Visualization: The Role of AI in Computer-Integrated Surgery

Mingxu Liu

Surgeons face stress and fatigue during surgical procedures, and computer-integrated surgery is developed to alleviate physical strain and improve precision. AI's advancement promises to further augment CIS by offering decision support, predictive analysis, and data integration, leading to better visualization and automation in operating rooms (OR). Future ORs will feature autonomous systems capable of advanced imaging, intuitive visualization, and precise robotic control.

My current research focuses on using AI to improve sensory and perceptual aspects of surgery, particularly in intra-operative guidance for orthopedic surgeries. Current orthopedic surgeries have limited transferability of data between pre-operative and intra-operative stages due to different imaging modalities and variations in patient anatomy. We applied AI to address these challenges through Deep Neural Networks that filter essential surgical data, learning-based image synthesis, and advanced image registration techniques that bridge gaps between modalities.

A significant application of this research is demonstrated in the treatment of the early-stage osteonecrosis of the Femoral Head (ONFH). Our team employed semantic segmentation on pre-operative MRIs to identify necrotic lesions and integrated this information into intra-operative fluoroscopic images, enhancing real-time visualization of ONFH during surgery. This approach underscores the synergy between AI, image processing, and engineering in medical applications. As a first-year Ph.D. student, I view these results as foundational for developing AI-enhanced surgical systems aiming to improve surgical imaging and visualization.

ABSTRACT 129

3D Mapping of Human Pancreas for Studying Microanatomical Structures Influenced by Type 1 Diabetes at Cellular Resolution

Yu Shen, Mia Grahn, Won June (Kevin) Cho, Bridgette Kim, André Forjaz, Casey Grubel, Maria Beery, Irina Kusmartseva, Pei-Hsun Wu, Mark Atkinson, Denis Wirtz, Ashley Kiemen

The anticipated escalation in the global prevalence of type 1 diabetes (T1D) is attributed to enhanced testing and healthcare accessibility. T1D is an autoimmune disease associated with the malfunctions of the pancreas' endocrine component, where the immune system attacks the insulin-producing beta cells in the islets of the pancreas and subsequently leads to uncontrolled blood glucose levels. Beta cell reduction is linked to interactions among various pancreatic structures, including the pancreatic acini, stroma, vasculature, and immune components. Presently, research is constrained to examining the spatial contribution of individual anatomical components. To investigate the interplay among multiple anatomical structures, we conducted histological analyses employing deep learning techniques to collectively reconstruct the spatial anatomical configurations of the human pancreas at the cellular resolution. Leveraging a tissue mapping platform called CODA, histological slides stained by hematoxylin and eosin (H&E) and immunohistochemistry (IHC) were automatically segmented based on tissue morphologies and immune labeling to evaluate the pathologic hallmarks related to inflammatory lesions near islets, exocrine components, and morphological changes on vasculatures. The spatial analysis of diabetic and nondiabetic pancreases at tissue and cellular levels provides a comprehensive understanding of the disease progression in T1D patients. Furthermore, we applied generative artificial intelligence models to transform H&E images to IHC images, aiming to extract molecular information with reduced reliance on manually stained histological slides. Current results indicate that advances in artificial intelligence can facilitate the discovery of autoimmune and pancreatic pathogenesis of T1D.

ABSTRACT 130

Personalized Nutritional Guidance: Aligning Preferences with Nutritional Needs

Farzin Ahmadi, Fardin Ganjkhanloo, Kimia Ghobadi

Inverse optimization is emerging as a useful approach for recovering personalized nutrition preferences. Unlike traditional optimization, which finds the optimal solution to meet constraints, inverse optimization determines the parameters to yield a predetermined solution. We present an inverse optimization-based recommendation model to provide individualized dietary guidance based on an individual's food preferences and health needs. Our models take individuals' food intake patterns over some time and provide recommendations based on similar patients, expert interventions, and personal preferences. We apply the methods to data from the National Health and Nutrition Examination Survey including roughly 10000 participants and publicly available commercial software data on nutritional intakes of individuals. For each individual, the inverse optimizer yields personalized recommended diets with similar foods and serving sizes to their reported intake but rebalanced to enhance nutritional quality according to expert-derived dietary guidelines. For a subset of patients grappling with hypertension, DASH recommendations are used that reduce suboptimal saturated fat (average 30%) and sodium intake (average 50%) and improve fiber and protein intake compared to self-selected diets. This is achieved while minimizing deviations from existing patient behavior by roughly 80% compared to benchmark inverse optimization models. This demonstration of inverse optimization-based models for nutrition guidance shows a promising ability to provide customized dietary advice tailored to individual preferences while still optimizing nutritional quality. The method can be extended to incorporate other conditions and personalized health factors including allergies, personal underlying chronic conditions, and any other form of dietary restriction or preference.

ABSTRACT 131

Vision-Based Mixed Reality Guidance for Accurate Navigation in Total Shoulder Arthroplasty

Wenhao Gu

Purpose: Mixed reality-guided surgery through head-mounted displays (HMDs) is gaining interest among surgeons. However, precise tracking of HMDs relative to the surgical environment is crucial for successful outcomes. Without fiducial markers, spatial tracking of the HMD suffers from millimeter- to centimeter-scale drift, resulting in misaligned visualization of registered overlays. Methods and workflows capable of automatically correcting for drift after patient registration are essential to assuring accurate execution of surgical plans.

Methods: We present a mixed reality surgical navigation workflow that continuously corrects for drift after patient registration using only image-based methods. We demonstrate its feasibility and capabilities using the Microsoft HoloLens on glenoid pin placement in total shoulder arthroplasty. A phantom study was conducted involving five users with each user placing pins on six glenoids of different deformity, followed by a cadaver study by an attending surgeon.
Results: In both studies, all users were satisfied with the registration overlay before drilling the pin. Postoperative CT scans showed 1.5mm error in entry point deviation and 2.4° error in pin orientation on average in the phantom study and 2.5mm and 1.5° in the cadaver study. A trained user takes around 90 seconds to complete the workflow. Our method also outperformed HoloLens native tracking in drift correction.

Conclusion: Our findings suggest that image-based drift correction can provide mixed reality environments precisely aligned with patient anatomy, enabling pin placement with consistently high accuracy. These techniques constitute a next step toward purely image-based mixed reality surgical guidance, without requiring patient markers or external tracking hardware.

ABSTRACT 132

Glucagon-Like-Peptide-1 Receptor Agonist Social Media Posts - Content Grouping and Sentiment Analysis with Artificial Intelligence

Aamir Javaid, Sruthika Baviriseaty, Harshita Kukreja, Chang H Kim, Seth S Martin, Francoise A Marvel

Background: Glucagon-like-peptide-1 receptor agonists (GLP-1RA) have surged in popularity in recent years, with discussions about their on-label and off-label use spilling into the public form. No study has analyzed online discussions about GLP-1RA.

Objectives: To analyze perceptions of GLP-1RA on social media.

Methods: We analyzed GLP-1RA related posts on Reddit between 5/28/2013-6/1/2023. All posts were identified that included generic or brand names of GLP-1RA. Post volume on Reddit was compared to search interest on Google over time. An artificial intelligence (AI) pipeline consisting of a semi-supervised natural language processing model (Bidirectional Encoder Representations from Transformers (BERT)), a dimensionality reduction technique, and a clustering algorithm was used to cluster posts into related topics. Discussion sentiment was classified using a pretrained BERT model and assessed qualitatively.

Results: 14,390 GLP-1RA related Reddit posts by 8,412 authors were identified. Most (94%) of posts were created after 2021, consistent with search interest trend on Google. We used the AI model to categorize posts into 30 topics which were hierarchically grouped into three overarching themes: insurance/cost, diabetes/diet, and medication-specific blogs. Posts were identified among communities for individuals with diabetes and obesity, as well as for diseases without an FDA-approved indication. Most posts had a negative sentiment.

Conclusions: Social media can be monitored with AI to generate insights on public perceptions of GLP-1RA. This may help guide patient-clinician discussions, inform strategies to address barriers to GLP-1RA use, and identify potential patient groups with high interest that warrant further study.

ABSTRACT 133

Perception, Extended Reality, and Their Transferability into Medical Environments

Alejandro Martin-Gomez

In the near future, Extended Reality (XR) will transform our daily lives and enhance our perception by integrating computer-generated content that co-exists with the physical world. This set of technologies, promises to revolutionize how we interact with our environment and has opened a new dimension of alternative realities and applications, including medical scenarios. My research interests focus on understanding the properties of human sensory and cognitive systems to create efficient, understandable, and transferable XR experiences. My long-term goal is to create XR systems that are as natural and intuitive as the physical world. In particular, I have a keen interest in developing perceptually-aware systems that integrate XR and artificial intelligence (AI) to enable the transferability of this technology into medical scenarios.

To achieve this goal, members of my lab are working on projects to enhance depth perception and situational awareness in multiple surgical scenarios. Major ongoing research projects at my lab include the development of systems to (i) provide in-situ visualization of multiple imaging modalities, pre-operative planning data, or navigation information combining XR and AI; (ii) enable multimodal visualization of diseases otherwise invisible when using traditional intraoperative imaging technologies in orthopedic surgery; or (iii) facilitate task completion during arthroscopic procedures by providing novel viewpoints from the perspective of surgical tools.

These projects involve collaborations with Professors Alex Johnson, Amit Jain, Julius Oni, and Mehran Armand, as well as with Xinrui Zou (Ph.D. candidate), Mingxu Liu (Ph.D. candidate), and Zheyuan Zhang (second-year Master's student).

ABSTRACT 134

Optimizing Patient Oxygen Saturation Estimation with Patient Health Information and Skin Tone Quantification

Orian Stapleton, Sreenidhi Sankararaman, Chao Cheng Chaung, Yolanda Su, Esanika Mukherjee, Jay Luo

BHypoxemic conditions, or medical problems stemming from low oxygen saturation, can result in half a million deaths annually in the US. Oxygen saturation, SaO2, can be measured directly by arterial blood. Although SaO2 is considered the 'gold standard' it is invasive, so blood oxygen saturation using light transmission from a pulse oximeter is often used as an approximation for SaO2. The measurement from pulse oximetry is called SpO2. Hidden hypoxemia, where SaO2 is recorded as less than 88%, but SpO2 from pulse oximetry shows between 92% and 96%, presents a significant concern in medicine. Individuals with darker skin tones often have an overestimation in SpO2 leading to higher instances of hidden hypoxemia in these populations. A method to accurately predict oxygen saturation given this overestimation on darker skin tones has not yet been refined. In many methods, race is often used as a proxy for skin tone but this poses problems as there can be great variation of skin tone even within a single race. Our solution is two-fold, first, we will develop a computational algorithm to obtain a better approximation for SaO2 using patient health information and SpO2. Secondly, we will develop, an algorithm that directly quantifies skin tone images to adjust SpO2 measurements. Ultimately, we want to mitigate the risk of hidden hypoxemia and ensure more equitable healthcare outcomes.

ABSTRACT 135

A brightness-aware method for cognitive load detection in tele-robotic surgery

Roger D. Soberanis-Mukul, Regine Büter, Rohit Shankar, Paola Ruiz Puentes, Ahmed Ghazi, Jie Ying Wu, Mathias Unberath

The automatic assessment of cognitive effort can enable different applications in telerobotic surgery, including enhanced surgical assistance and personalized training programs. While pupillometry-based methods have been proposed for unobtrusive cognitive load assessment, their application in surgery is limited, given the pupil's sensitivity to light, which masks cognitive load signals. As pupil diameter can be affected by cognitive load and brightness, the development of methods able to disambiguate these signals is essential for cognitive load detection in unconstrained scenarios. This work introduces a personalized brightness-aware cognitive load pupil response model that, combined with gaze entropy, is employed to detect cognitive load using a random forest classifier. We compared the model against two baseline metrics (BCPD and CPD) on an in-house dataset generated by a user study with the da Vinci Research Kit on 17 users. The dataset was obtained under brightness variations to evaluate the light-awareness capability of the models. Our method achieves a 0.78 true positive rate compared with 0.57 and 0.64 obtained by the baselines, showing its ability to estimate cognitive effort under unconstrained brightness scenarios. We hope our model inspires further development that allows to capitalize on the benefits of cognitive load detection in tele-robotic surgery to enhance patient outcomes and surgical performance.

ABSTRACT 136

A Comprehensive Seizure Detection, Localization, and Classification Tool for Epilepsy Monitoring

Amir Hossein Daraie, Luis A Sanchez, Lynette Talley, Adam S Charles, Joon Yi Kang, Sridevi V Sarma

Epilepsy is characterized by recurrent seizures varying in severity. Traditional seizure detection methods involve time-consuming intracranial EEG analysis, prone to errors and misinterpretations, with challenges like limited expert availability, especially in developing countries. Consequently, there's a demand for efficient, automated methods. Machine learning (ML) algorithms in EEG data classification, despite their promise, require extensive training datasets and lack interpretability. Accurately localizing the seizure onset zone (SOZ) is also crucial, particularly in drug-resistant epilepsy, but current methods are limited, indicating a treatment gap in epilepsy.

This study develops a diagnostic tool using intracranial EEG (iEEG) data for comprehensive seizure localization without training data. It's interpretable, applicable across ages, capable of real-time processing, and noise-resistant. The tool utilizes the source-sink (SS) metric from dynamical network models to quantify each node's influence within the network. During seizures, epileptogenic regions become strong, static sinks, losing natural variability, which is tracked using spectral entropy. This method detects seizures and categorizes them, offering detailed characterization.

Seizure localization involves identifying the SOZ. Utilizing Bayes' theorem, the process systematically updates the likelihood of each channel being the SOZ based on entropy drops during seizures. Our system, tested on 1000 hours of iEEG from five patients, achieved a sensitivity of 97.43% and precision of 92.48%, with 89.41% overall accuracy.

In conclusion, our algorithm aids clinicians in accurately localizing the EZ, improving surgical outcomes and personalized treatment, enhancing patient monitoring and decision-making. However, 39.81% of seizures were missed by the monitoring unit, highlighting the need for further improvement.

ABSTRACT 137

Vision-Based Navigation for Next Generation Endoscopic Sinus Surgery

Jan Emily Mangulabnan, Roger Soberanis, Timo Teufel, Manish Sahu, Jose L. Porras, S. Swaroop Vedula, Masaru Ishii, Gregory Hager, Russell H. Taylor, Mathias Unberath

Endoscopic navigation guides surgeons through intricate anatomies to improve patient outcomes during intervention. Current approaches rely on external trackers and preoperative computed tomography (CT) to enable real-time intraoperative navigation based on patient-specific anatomy. However, these navigation systems are limited in their ability to reflect the anatomical changes brought by surgery and require additional hardware that may negatively impact clinical workflow.

Our work investigates vision-based methods to provide surgeons with a precise understanding of the current anatomical state at no additional hardware cost. We propose a two-step approach to reconstruct and dynamically update 3D representations of the sinus using computer vision and deep learning techniques with endoscopic video.

We quantitatively evaluate our methods by obtaining endoscopic video paired with optical tracking and high-resolution CT from a simulated endoscopic sinus surgery on cadaveric specimens. Results show that our proposed image-based algorithms generate 3D sinus structures in agreement with the ground-truth CT. Our reconstructions yield an average point-to-mesh error of 0.91 mm and our update method has shown to improve accuracy during surgical progression, demonstrating the feasibility of our approaches for sinus navigation. We further utilized this dataset to assess individual components and identify critical aspects of our methods that contribute to the precision of our results, guiding our future work to enable clinical application of an endoscope-centered navigation system. Such a system would provide surgeons with a precise understanding of the current anatomical state at no additional hardware cost, paving the way towards a digital twin paradigm for sinus surgery.

ABSTRACT 138

Identifying and classifying medications for hypertension in the electronic health record

Amanda Chuk, John Scott, Ching-Huan Wang, Michael Chiu, Lisa Yanek, Jodi Segal, Samantha Pitts

Background: Extracting medications from clinical datasets is challenging due to the number of medication names and formulations for each ingredient. Epic uses a proprietary system to classify medications and not all medications can be readily mapped to a standard nomenclature such as RxNorm.

Methods: We sought to develop a standards-based approach to identify and extract medications from Epic, using antihypertensives as exemplars. We identified antihypertensive ingredients using the Anatomical Therapeutic Chemical and Established Pharmacologic Class classification systems. We then queried the National Library of Medicine RxNav application programming interface to identify all corresponding RxNorm codes. We identified antihypertensive medications in the EHR based on RxNorm codes combined with a string search for ingredient names ("NLM pathway") and compared this to classification by the EHR proprietary system, First Data Bank ("FDB pathway").

Results: For medication classes tested (ACE inhibitors, calcium channel blockers), the NLM pathway identified all medications identified by the FDB pathway plus additional relevant medications. Medications identified by only the NLM pathway often included orders specific to a Johns Hopkins care setting or medication name without strength. The NLM pathway required clinical review of a small set of ingredients – rather than a longer list of medications.

Conclusion: The NLM pathway identified all medications identified by the FDB pathway with reduced need for clinical curation.

ABSTRACT 139

Prescribing of Evidence-based Medications for the Prevention of Adverse Cardiovascular Events and Progression of Chronic Kidney Disease Among Patients with Diabetes

Samantha Pitts, Lisa Yanek, Justin Wu, Alisa Mayas, Erin Michos, Nes Mathioudakis, Nisa Maruthur

Background: Atherosclerotic cardiovascular disease (ASCVD) is the leading cause of mortality in the US. Among patients with diabetes and established or high risk of ASCVD, there is strong evidence for reduction of cardiovascular outcomes, including cardiovascular and all-cause mortality, with the use of glucagon-like peptide-1 receptor agonists (GLP1 RA) and sodium-glucose transport protein-2 inhibitors (SGLT2i). SGLT2i have also demonstrated benefits in patients with heart failure (HF) and chronic kidney disease (CKD).1 As a result, the ADA recommends GLP1 RA and/or SGLT2i use as first line agents independent of the need for glycemic control in populations with ASCVD, HF, and CKD.2 The proportion of patients with type 2 diabetes in primary care at Hopkins receiving GLP1 RA and SGLT2i is unknown.

The overarching aim of this study is to understand gaps in the prescribing of GLP1 RA and SGLT2i among patients with diabetes in primary care at Johns Hopkins to inform an intervention to improve their utilization and reduce cardiovascular outcomes among these high-risk patients.

Methods: We identified patients with at least one visit to a Johns Hopkins primary care location in the prior 12 months with type 2 diabetes, determined by at least one visit diagnosis for type 2 diabetes (E11 – E14). We further classified patients with diabetes as having an indication for a GLP1 RA or SGLT2i if they had at least one visit diagnosis for ASCVD (I20 - 25), CKD (N18) or HF (I50). We defined patients as having been prescribed a GLP1 RA or SGLT2i if they had at least one medication order identified.

Results: Among 183,203 patients with a visit in primary care in the prior 12 months, 26,560 (14.5%) had type 2 diabetes, of whom 11,722 (44.1%) had one of the three co-morbid conditions, indicating high risk for major cardiovascular adverse events. ASCVD was most common [7862 (29.6% of all patients with diabetes)], followed by CKD [6508 (24.5%)], and HF [3862 (14.5%)]. Among patients with diabetes and one of the three co-morbid conditions, 5885 (50.2%) had ever received a GLP1 RA or an SGLT2i.

Conclusion: Only half of patients with diabetes in seen in primary care at Hopkins in the past 12 months have any medication order for evidence-based medications for the prevention of major adverse cardiovascular events and progression of chronic kidney disease. Additional study is necessary to refine the definitions of the target populations (e.g., CKD with estimated glomerular filtration rate <60 or proteinuria), examine current use of these medications, and to understand barriers to prescribing to guide the development of interventions to improve the use of SGLT2i and GLP1 RA among high-risk populations with diabetes.

ABSTRACT 140

The transcriptomic cortical alterations in profound hearing loss

Xuan Wang, Itzamná Sánchez-Moncada, Bo Ao, J. Tilak Ratnanather, Francis A. M. Manno

The mechanisms driving hemispheric asymmetry are not completely understood, i.e. why does language predominately develop in the left hemisphere. We determined if sensory deprivation due to hearing loss alters dominant left > right patterning of asymmetry by analyzing MRI volume-based morphometry, shape metrics, and transcriptomics. We recruited a homogeneous group of children (n=42) with a pure profound sensorineural hearing loss (≈ 90 db), (n = 18 bilateral, prelingual), unilateral hearing loss (left n= 10, right n= 14, perilingual), in addition to 43 age and sex matched controls (range 6 months to 18 years). Asymmetry metrics were significantly different between hearing loss groups and controls. A two-way ANOVA with HL group and hemisphere as factors found an effect for HL group for the MFG and STG, and an effect for hemisphere for STG. No interaction effect was observed by HL group X hemisphere. Several genes were of considerable interest in the cortical alterations in HL: 1) NLGN3- Neuroligin-3 (cell adhesion molecule - autism spectrum disorder), 2) MAP6- Microtubule Associated Protein 6 (signalling for axonal growth), and 3) SNCA - alpha-synuclein (related to Alzheimer's). Shape-transcriptomic metrics revealed shifts could be due to the brain twisting around the neuroaxis to compensate for altered hearing elicited by different sensory input. Our results appear to give divergent evidence for neurodevelopmental maturational trajectories as purported by the Geschwind–Galaburda hypothesis. Our results support that sensory sculpting of the auditory cortex due to sided input leads to unique hemispheric lateralization patterning in hearing loss.

ABSTRACT 141

Programming soft matter voxel interface properties in extrusion 3D printing

Daniel C. Ames, Sarah Propst, Aadarsh Shah, Jochen Mueller

Interfaces play a key role in determining the mechanical properties and macro behaviors of multi-material structures. It can be difficult to fabricate soft matter and architected materials with interfaces using additive manufacturing, as multi-material print systems are limited in printing structures with widely differing aspect ratio features. We propose a method of 3D printing multi-material soft matter through the co-extrusion of filaments and interfaces, where the interfaces are dynamically controllable with differing mechanical, electrical, and optical properties during print. Consequently, flexible touch sensors and other applications can be printed with tailored interfacial properties. This method opens the door to a variety of material types with varied properties that can be rapidly printed together to create soft matter used in biomedical, aerospace, and other engineered structures.

ABSTRACT 142

Effect of implicit bias on performance of unbiased models for video-based surgical skill assessment

Nanthini Narayanan, Divyasree Sasi Kumar, S. Swaroop Vedula, Shameema Sikder, Vishal Patel

Video-based surgical skill assessment (VBA) is crucial for surgical education and improved patient outcomes. Machine learning (ML) techniques allow for objective assessment of surgical skill. ML models for VBA should be thoroughly evaluated for adoption into routine practice. While it is intuitive that training models with incorrect ground truth leads to useless models, we investigate the effect of evaluating unbiased models with erroneous ground truth in the test set. Implicit biases within raters are an important source of these errors in the test set. We train the current state-of-the-art VBA model on unbiased data and test it on test sets with different degrees of implicit bias from simulated and real-world data. We perform sensitivity analysis to calculate the true metrics of the model and quantify the difference in performance due to implicit bias. In the simulated test sets, we quantify an average 8% to 17.1% decrease in the difference between observed and true Area Under the Curve (AUC) scores. Even with a theoretically perfect model, we observe an average decrease of X% in AUC scores with a 10% increase in bias. To validate these findings in real-world scenarios, we used test sets from human raters recruited on MTurk. Biased test sets are associated with a 25.9% decrease in model performance (AUC). Even when ML models are trained on unbiased data, the presence of implicit bias in test datasets can significantly impact their performance.

ABSTRACT 143

Data-driven simulation quantifies how lymphocyte motility drives immune interactions

Nikita Sivakumar, Chanhong Min, Kibaek Choe, Wendy Beguelin, Feilim Mac Gabhann, Jude M. Phillip

Cell motility enables lymphocytes to discover pathogens and engage in key cellular interactions that mediate the immune response. Lymphocyte motility is particularly important to the functioning of the germinal center reaction, a multicellular system that produces high-affinity antibodies in response to infection. Within the germinal center (GC), B- and T-cells engage in interactions that drive antibody affinity maturation and function. While cell motility facilitates critical interactions between B- and T-cells, the relationship between specific cell motility parameters and cell-cell interaction dynamics is unclear. Moreover, recent work has demonstrated that cancer-associated mutations and aging can alter GC lymphocyte motility, but the emergent impact of these perturbations on the dynamic interactions that drive GC function is difficult to measure experimentally. Here, we built a computational framework to systematically explore how single-cell motility impacts cell-cell interaction dynamics. First, we quantified eight distinct lymphocyte motility patterns from intravital microscopy videos of mouse GCs and found that T-cells and B-cells have distinct signatures of these patterns. Then, we developed and parameterized a multicellular agent-based model to explore how differential cell motility parameters can recreate the observed motility patterns, and how these parameters affect cell-cell interaction dynamics. Our simulations show that certain combinations of motility parameters maximize interaction dynamics within this system. These results identify potential cellular engineering targets to enhance germinal center function. Moreover, our model serves as a broader framework to study how single-cell motility alters interaction dynamics in a wide variety of multicellular, biological systems.

ABSTRACT 144

m6A mRNA modifications regulate embryonic heart maturation

Shunyao Lei, Harshi Gangrade, Sheetal Bajpayi, Myo Htet, Sean Murphy, Edwin Yoo, Navid Koleni, Emmanouil Tampakakis

Congenital heart disease (CHD) are the most prevalent birth defects, and they are primarily attributed to perturbations in the regulatory processes governing heart development. While genetic mutations in transcriptional factors and morphogens account for a minor portion of CHD, epigenetic and epitranscriptomic mechanisms add an additional layer of regulation beyond traditional genetics. Moreover, mRNA modifications may reconcile disparities between gene expression and translation, a domain largely unexplored in heart development. To investigate post-transcriptional regulation during cardiogenesis, we focused on m6A mRNA modifications, the most abundant post-transcriptional regulators of mRNA dynamics. First, mass spectrometry and transcriptomic analyses in mice showed that m6A mRNA peaks around embryonic day 12.5. Disruption of methyltransferase like-14, a major writer of m6A, in cardiac progenitor cells resulted in reduced cardiac function and late embryonic lethality. Mutant hearts displayed ventricular non-compaction, reduced cardiomyocyte proliferation, and increased apoptosis. Single-cell transcriptomic analysis indicated shifts in cardiomyocyte specification, and disruptions of metabolism- and translation-related genes. Similar metabolic effects were corroborated by proteomics. Multiple m6A peaks were observed on Ying Yang 1, a transcription factor governing mitochondrial biogenesis and glycolytic metabolism. To investigate further the effects of m6A mRNA in embryonic cardiomyocytes, we engineered a novel CRISPR-based system to specifically target mRNA transcripts for m6A modifications in stem cell derived-cardiomyocytes. In summary, our findings underscore the key role of m6A mRNA modifications as key regulators of cardiomyocyte maturation, allowing for smooth transitions across critical developmental stages. Additionally, targeted epitranscriptomic modifications render potentials for fine-tuning gene expression in cardiac development and disease.

ABSTRACT 145

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ABSTRACT 146

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ABSTRACT 147

Automated Fall Risk Assessment and Prevention Tool (FallPRO), Improving Prediction and Efficiency

Fardin Ganjkhanloo, Erik Hoyer, Daniel Young, Anton Dahbura, Kimia Ghobadi

Falls are a major source of preventable injury and death for hospitalized older adults. Current fall risk assessment and prevention practices are primarily conducted manually by nursing staff. This current practice has limitations including being time consuming, subjective, prone to human error, and does not utilize real-time patient data. To address these gaps, we are developing an automated, data-driven tool called FallPRO that integrates fall risk assessment and then suggests prioritized prevention actions. We use mathematical optimization and artificial intelligence techniques to analyze patient demographics, mobility assessments, comorbidities, medications, and other electronic health record data to generate a real-time, individualized fall risk score. We then identify and prioritize evidence-based prevention interventions tailored to each patient's risk factors. This dynamic risk scoring model suggesting prevention intervention prioritization based on specific risk factors will integrate into the FallPRO tool. The initial results of our models assessing risk of fall show promise in improving upon current practices. Our cross-disciplinary team combines clinical expertise in Physical Medicine and Rehabilitation with technical skills in healthcare analytics, predictive modeling, and optimization. This project lays the groundwork for reducing preventable falls and related costs, improving nursing efficiency, and enhancing patient outcomes. It has the potential for broader implementation and adaptation to other patient safety issues.

ABSTRACT 148

Genetic medicine practices in primary care settings at Johns Hopkins Medicine

Michelle Nguyen, Carolyn Applegate, Lisa Renee Yanek, Samantha Irene Pitts, Cynthia Anne James, Ada Hamosh, Casey Overby Taylor

An individual's primary care provider (PCP) is often their first point-of-contact with healthcare resulting in PCPs becoming gatekeepers to genetic services [1]. PCPs, however, report a lack of familiarity with genetic testing and confidence collecting adequate family health history (FHx) needed to make genetic testing decisions [2]. These reported barriers may impact genetic medicine utilization in a primary care setting. As we strive to deliver care that aligns with precision medicine goals, we first need to understand the current genetic medicine practices in primary care. The objective of this study was to investigate the ordering of genetic tests by PCPs and FHx documentation in a cohort of patients from the Johns Hopkins Precision Medicine Center for Excellence for Adult Primary Care (APC-COE) who had at least one visit at any Johns Hopkins Medicine primary care location since 7/1/2016 (n=361,486). First, we performed descriptive statistical analysis for this population. We found a high prevalence of structured FHx data captured among patients included in the registry, with 92.1% of individuals having at least one family history entry in structured data. However, among patients with structured FHx, we discovered variability in the completeness of FHx data with respect to number of reported family member-condition concept pairs and age of onset and agreement between providers and patients. To further investigate genetic test ordering practices, we selected nine genetic tests commonly ordered in the EHR. Next, a fter excluding genetic test orders by non-primary care specialty providers, we found that 463 out of 984 genetic test orders were made by clinicians from primary care departments (Adult Medicine, Family Medicine, Internal Medicine, and Pediatrics). Chromosome microarray was the most frequently ordered test (176 tests, 38% of total count) followed by other (124 28.6%) and exome sequencing (21.6%). This work provides preliminary insight into genetic practices within a Johns Hopkins Medicine primary care settings and provides baseline data prior to developing interventions to better integrate genetic medicine into primary care.

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2. Sharma Y, Cox L, Kruger L, Channamsetty V, Haga SB. Evaluating Primary Care Providers' Readiness for Delivering Genetic and Genomic Services to Underserved Populations. Public Health Genomics. 2021 Sep 7:1-10. doi: 10.1159/000518415. Epub ahead of print. PMID: 34515218.

ABSTRACT 149

Electronic feedback on clinical reasoning for hospitalists: a pilot study

Susrutha Kotwal, Karthik Meiyappan Udayappan, Nikhil Kutheala, Catherine Washburn, Caitlin Morga, Suzanne Grieb, Scott Wright, Gurpreet Dhaliwal

Background: American hospitals annually see an estimated 250,000 diagnostic errors, many attributable to faulty clinical reasoning. Feedback on the diagnostic process improves clinical reasoning. Limited time and negative reactions constrain delivery and receipt of feedback. The shift to asynchronous digital communication and electronic learning suggests that electronic feedback ("e-feedback") could overcome these constraints.

Purpose: We developed e-feedback for hospitalists around care escalations (ICU transfer, rapid responses) then qualitatively evaluated their satisfaction with, and commitment to change in practice, based on the feedback.

Methods: Our qualitative study was conducted at one academic medical center February-June 2023. Participants were adult physician and advanced practice provider (APP) hospitalists. Using the Safer Dx framework, a team of two hospitalists, one senior internal medicine resident, and one clinical nurse reviewed charts weekly after escalations of care. Timely, confidential feedback was emailed via REDCap; hospitalists then rated their satisfaction, reasons for satisfaction/dissatisfaction, and plans to modify their practice based on this e-feedback. Hospitalists' open-ended comments were analyzed; analysts developed and refined a codebook based on content of comments; this was applied to all comments. Codes were aggregated into themes telling a coherent story.

Results: 49/58 (84%) hospitalists participated; 78% physicians, 22% APPs. 105/124 (85%) e-feedback surveys were returned. 70 (67%) were rated highly satisfied, 24 (23%) were rated moderately satisfied, 11 (10%) were rated not satisfied.

Conclusions: Hospitalists appreciated the e-feedback process, reflected on the diagnostic process, and identified future behavior changes. Further studies are needed to see whether e-feedback enhances hospitalists' clinical reasoning.

ABSTRACT 150

Characterizing cell-type spatial relationships across length scales in spatially resolved omics data

Rafael dos Santos Peixoto, Brendan F. Miller, Maigan A. Brusko, Lyla Atta, Manjari Anant, Mark A. Atkinson, Todd M. Brusko, Clive H. Wasserfall, Jean Fan

Advancements in spatially resolved omics have incorporated the spatial dimension into single-cell molecular profiling. Applications of such technologies offered the opportunity to characterize spatial niches where specific cell-type groups colocalize, enhancing our understanding of tissue organization and function. These colocalizations occur at distinct spatial scales to enable different potential cellular interactions. To quantify such relationships, we present CRAWDAD, Celltype Relationship Analysis Workflow Done Across Distances, implemented as an open-source R package. CRAWDAD identifies cell-type colocalization or separation across spatial scales. It uses a binomial proportion testing framework to compute the statistical enrichment of each cell type against the permutated null background within the reference cell type's neighborhood, controlling for the presence of local structures within tissues. By permuting at different spatial scales, cell-type spatial relationships do not change as our field of view is broadened to a larger tissue section inclusive of other cell types. We validated CRAWDAD on simulated data, recapitulated expected cell-type relationships in a Slide-seq mouse cerebellum dataset, and identified colocalizations at different scales in a seqFISH mouse embryo, corroborating with the cells' developmental origins and functions. CRAWDAD consistently revealed which cell types colocalized to form the white and red pulp when analyzing multiple CODEX spleen samples from different individuals. Furthermore, CRAWDAD employs the same statistical framework to subset cell types based on their enrichment around others, extending the general pairwise analysis. We anticipate that CRAWDAD will be applicable to diverse spatial omics technologies, revealing new functional structures and leading to a deeper understanding of tissue composition.

ABSTRACT 151

Modeling Magnesium: Optimizing Implants for Superior Bone Fracture Healing

Rida Chowdhury, Camryn Bryum, Tunde Ayodeji, Sreenivas Raguraman, Timothy Weihs

The conventional approach to treating bone fractures relies on the use of titanium and stainless-steel screws and plates. Despite their widespread use, these traditional implants present challenges, such as the need for a secondary surgery for removal post-healing and inherent dissimilarities in properties when compared to bone, leading to stress-shielding. Considering these limitations, there is growing interest in magnesium alloys as a viable alternative due to their demonstrated biocompatibility, biodegradability, and bone-like mechanical properties. While certain magnesium-based implants have received market approval, a substantial gap remains in our understanding of optimal alloys and implant parameters. A particularly intriguing avenue of exploration is the concept of cannulated (hollow) magnesium-based screws, which, if successful, could not only maintain mechanical properties but also serve as carriers for antibiotics to enhance the healing process—a feature explored in traditional implants but not yet in magnesium alloys. To address these gaps, this study employed computer-aided design and finite element analysis to model and compare cannulated and solid screws. The screws, composed of materials including stainless steel, titanium alloy, pure magnesium, and magnesium alloy AZ63A, were simulated under various loads to understand their performance in different parts of the body. The results from this investigation revealed information critical to understanding the materials and design parameters required for optimal magnesium-based implant performance, highlighting the untapped potential that lies in cannulated screws but also the challenge of providing sufficient support due to their lower resistance to deformation when compared to traditional implants.

ABSTRACT 150

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ABSTRACT 152

Investigating immunologic mechanisms for the association between IBM and RA

Tara Fallah Rastegar, Hong Wang, Brit Adler, Jemima Albayda, Julie Paik, Christopher Mecoli, Eduardo Gomez Banuelos, Andrew Mammen, Tom Lloyd, Lisa Christopher, Erika Darrah, Eleni Tiniakou

Background: Inclusion body myositis (IBM) is a distinct type of inflammatory myopathy of unclear etiology with a com-bination of autoimmune and myodegenerative components. While typical myositis-associated antibodies are absent in IBM, the presence of other disease-associated antibodies, like rheumatoid arthritis, is unknown.

Objective: We aimed to investigate the presence of an autoimmune response against autoantigens associated with rheu-matoid arthritis. We screened for anti-cyclic citrullinated peptide (anti-CCP) and anti-peptidylarginine deiminase-4 (anti-PAD4) antibodies in patients with IBM.

Method: Serum from patients with IBM (n=151), healthy controls (HC) (n=67), were tested for anti-cyclic citrullinated peptide (CCP) and anti-peptidyl-arginine deiminase 4 (PAD4) antibodies. The antibody prevalence was analyzed using Chi-squared test and Mann-Whitney U-test. The degree of correlation between anti-CCP and anti-PAD4 was determined by Pearson correlation test.

Result: 12 out of 151 patients with IBM (7.94%) tested positive for anti-CCP antibodies, while none of the 67 HC showed positivity (0%, P=0.02). Regarding anti-PAD4 antibodies, 22 out of 151 patients with IBM (14.56%) and 6 out of 67 healthy controls (7.89%) were positive, showing no significant difference (p=0.2). The median levels of anti-CCP and anti-PAD4 antibodies did not significantly differ between the patients with IBM and the healthy controls. Interestingly, we ob-served a moderate correlation ($r=0.478$, $p<0.001$) between anti-CCP and anti-PAD4 in patients with IBM. Among the IBM patients positive for anti-CCP antibodies, a subset of four patients also had a concurrent diagnosis of rheumatoid arthritis (RA).

Conclusion: Our findings revealed statistically significant prevalence of anti-CCP antibodies in patients with IBM, indi-cating that citrullination of antigens may contribute to the pathogenesis of a subset of IBM patients. The presence of anti-CCP antibodies in IBM patients may serve as a potential marker for the development of rheumatoid arthritis in this spe-cific population. Further research is warranted to gain a better understanding of the underlying mechanisms and clinical implications of this association. Such investigations will also help explore potential implications for the management and treatment strategies for patients with IBM and concurrent rheumatoid arthritis.

ABSTRACT 153

Autism Recovery using the Specific Carbohydrate Diet: Literature Review and Case Report

Angela Taylor

Here we review numerous publications which have documented the effectiveness of medical nutrition therapy in alleviating autism symptoms. This particular case study highlights the journey of a 4-year-old boy with autism and his improvements following the adoption of the Specific Carbohydrate Diet (SCD). After following the SCD for 19 months he was considered recovered from autism, and his individualized education program (IEP) was dissolved. Further investigation is warranted to understand the relationship between gastrointestinal issues, intestinal permeability, nutritional interventions, and autism spectrum disorders.

ABSTRACT 154

Rapid Sensing System for Personalized Treatment of Diabetic Retinopathy

Jeongyun Kim, Geonhui Lee, Aimee Arash-Ajayi and Sangmoo Jeong

Diabetic retinopathy (DR) is a highly prevalent eye condition in diabetic patients that can lead to vision impairment and blindness. The molecular pathophysiology of DR vastly varies among patients and consequently leads to different responses to drugs. Therefore, to transition from conventional trial-and-error treatment to a more effective and efficient approach of personalized treatment, molecular analysis of biomarker proteins is needed. While current molecular analysis methods have long turnaround times that are not practical in clinical settings, we propose a rapid and sensitive immunoassay-based sensing system that can be used at point-of-clinic with minimum resources. We aim to detect the concentrations of four different biomarkers of DR using the sensing system. Two key approaches in achieving high sensitivity and short assay time is to enhance the signal readout through amplification and increase the binding probability of immunoassay components. The final system will be built into a easy-to-use and compact platform of either electrochemical or optical sensing.

ABSTRACT 155

Virtual Health Coaching in a Home-Based Cardiac Rehabilitation Program

Asma Rayani, Mansi Nimbalkar, Chang H. Kim, Mansi Nimbalkar, Nino Isakadze, Ali Kassamali, Jooyoung Ryu, Claire Zhang, Zane MacFarlane, Yumin Gao, ScM, Jie Ding, PhD, Ashley Broderick, Alex Bush, Jeanmarie Gallagher, Preeti Benjamin, Brittany Neigh, Kerry J. Stewart, Lena Mathews, Erin Spaulding, Seth S Martin, *Francoise A. Marvel (corresponding author)

Background: To improve accessibility and cost-effectiveness of Cardiac Rehabilitation (CR), we developed a home-based CR program based on the Corrie Health platform that consists of a mobile application, wearables (smartwatch and blood pressure monitor), clinician dashboard, and telehealth coaching sessions to improve patient engagement and education, and reinforce holistic CR.

Methods: Participants were enrolled in our pilot project from November 2022 to February 2023. They were offered 12 weekly home-based health coaching sessions and integrated outpatient CR with a patient-facing mobile app (Corrie) integrating wearable technology. We analyzed the topics discussed during each coaching session.

Results: Among 11 participants, there were 7 males (64%), with a mean age of 61.1±7.4 years, of diverse race/ethnicity (54.6% Caucasian, 18.2% African American, 9.1% Asian, 9.1% Hispanic, and 9.1% Other). On average, participants attended a mean of 6.5 coaching sessions, with 'Exercise' being discussed in a mean of 5.8 sessions. 'Technology,' 'BP,' and 'HR' were discussed in a mean of 4.5, 4.4, and 4.3 sessions, respectively. 'Diet,' 'Cholesterol,' and 'Weight' were discussed in 3.7, 3, and 2.5 coaching sessions on average.

Conclusion: We demonstrated a comprehensive approach to home-based CR that fostered discussions encompassing all facets of cardiovascular health, offering CR through a virtual medium.

ABSTRACT 156

B cell-mediated antigen presentation promotes adverse cardiac remodeling in chronic heart failure

Jana P. Lovell, Carolina Duque, Sylvie Rousseau, Aashik Bhalodia, Kevin Bermea, Charles D. Cohen, Marcelle Dina Zita, Luigi Adamo

Introduction: Activation of the "cardio-splenic axis" by acute cardiac injury promotes adverse cardiac remodeling and ischemic heart failure. B lymphocytes account for more than half of splenic immune cells, but their potential role in the cardio-splenic axis of heart failure remains unexplored.

Methods and Results: We subjected mice to permanent coronary ligation (AMI) to induce ischemic heart failure. Four weeks after AMI or sham surgery, we isolated splenic B cells and transferred them into healthy wild-type mice. Eight weeks after the adoptive transfer, we assessed adverse cardiac remodeling via echocardiography, gravimetric analysis, and histology. Adoptive transfer of splenic B cells from mice with ischemic heart failure was sufficient to induce adverse cardiac remodeling in recipient animals. Adoptively transferred splenic B cells were found in the recipients' spleen, blood, and heart 8 weeks post-transfer. Single cell sequencing of splenic B cells post-AMI revealed significant upregulation of signaling pathways related to antigen processing and presentation, without clonal expansion of B cells. Therefore, we developed transgenic mice with B cell-specific MHC class II deletion and repeated our initial adoptive transfer studies. Splenic B cells deficient in MHC class II from post-AMI mice did not induce adverse cardiac remodeling in naïve recipient mice. Single-cell sequencing of peripheral blood B cells was also performed in post-AMI human patients and healthy patients, and showed similar dysregulation of antigen-presenting and presentation in B cells following AMI in humans.

Conclusions:
Following acute myocardial injury, splenic B cells recirculate along the cardio-splenic axis and contribute to adverse cardiac remodeling via MHC class II-mediated antigen presentation.

ABSTRACT 157

Simulated Microgravity Attenuates Myogenesis and Contractile Function of 3D Engineered Skeletal Muscle Tissues

Zhanping Ren, Eun Hyun Ahn, Minjae Do, Devin B. Mair, Amir Monemianesfahani, Peter H.U. Lee, and Deok-Ho Kim

The growing interest in bioengineering more in vivo-like three-dimensional functional tissues has led to novel approaches to the biomanufacturing process as well as expanded applications for these unique tissue constructs. Microgravity as seen in spaceflight is a unique environment that may be beneficial to the tissue-engineering process but cannot be completely replicated on Earth. Additionally, the expense and challenges of conducting biological research in space make bioengineered microphysiological systems an attractive research model. In this review, we summarize published research that exploit real and simulated microgravity to improve the biomanufacturing of a wide range of tissue types as well as those studies that use microphysiological systems, such as organ/tissue chips and multicellular organoids, for modeling human diseases in space. We discuss real and simulated microgravity platforms and their applications in tissue-engineered microphysiological systems across three main topics: 1) application of microgravity conditions to improve the biomanufacturing of tissue constructs, 2) the use of tissue constructs fabricated in microgravity conditions as models for human diseases on Earth, and 3) investigating the effects of microgravity on human tissues using biofabricated in-vitro models. These current achievements represent important progress in understanding the physiological effects of microgravity and exploiting its advantages for tissue biomanufacturing.

ABSTRACT 158

Sugars : O-GlcNAcylation, Ketones and the Cardiometabolic Substrate Switch

Gabriel-Lopez Cecetaite, Priya Umapathi

Obesity is a fast-rising co-morbidity and a major contributor of heart failure (HF). Obesity-related changes in the heart include increases in fatty acid oxidation/decrease in glucose oxidation/glycolysis. Dietary modification in obesity has been proposed as a therapy and ketone diets are being tested in clinical trials. Hearts from obese patients have elevated levels of O-GlcNAcylation. Our lab has previously shown, in a murine model, elevated O-GlcNAcylation causes cardiomyopathy. Increases in the O-GlcNAcase and attenuated O-GlcNAcylation rescue cardiac dysfunction. Preliminary data from this model suggest substrate utilization are altered and may represent a molecular intersection point for ketone metabolism. We hypothesized excessive O-GlcNAcylation impairs energetics through inefficient substrate utilization in the failing heart, ketones provide more efficient fuel. We studied the use of a ketone (KD) vs. control diet (CON) in a murine high fat diet (HFD) cohort. We found HFD mice lost more body weight ($p<0.05$) and had smaller heart weights. Echocardiographic parameters noted no difference in ejection fraction ($p>0.5$) and less left ventricular hypertrophy ($p<0.05$) in the KD mice. Protein levels of OGT and OGA were similar between groups, total O-GlcNAc modified levels were higher in the KD group ($p<0.01$) compared to CON but lower than HFD only. Decreased levels of the pro-hypertrophic Yes Associated Protein was found in the KD cohort compared to CON ($p<0.05$). Our preliminary data suggest HFD treated with KD was associated with greater weight loss, decreased hypertrophy and O-GlcNAcylation. These results are hypothesis generating and suggest attenuation of O-GlcNAcylation and cardio-metabolic substrate switch may represent a HF rescue therapy in patients.

ABSTRACT 159

A Novel Mediator of Cardiac Hypertrophy and Heart Failure - Modulation of YAP via O-GlcNAcylation in the Heart

Priya Umapathi

Introduction: Heart failure (HF) is a growing pandemic, strongly tied to cardiac stressors and interlinked with increased levels of O-beta-N-Acetylglucosamine modified proteins in the heart (OGN). OGN levels are determined by the net activity of two enzymes, OGT and OGA. We have previously shown murine myocardial OGT overexpression (OGT TG) have pathological cardiac hypertrophy. Myocardial OGA overexpression (OGA TG) have attenuated OGN, interbreeding OGT TG with OGA TG normalizes OGN levels and rescues the OGT TG phenotype. The heart utilizes multiple adaptive mechanisms to maintain cardiac function and our data suggest a novel connection between OGN and YAP activation in the heart.

Objectives: Test if O-GlcNAc activates YAP in the heart.
Methods: We quantified levels of activated YAP protein and gene expression in hearts from WT, transgenic cohorts and OGA TG mice protected against hypertrophy from transaortic constriction (TAC). We used an adenoviral YAP/TEAD expression reporter to test activation of YAP in cardiac cells exposed to increased O-GlcNAcylation.

Results: We found increased, activated (nuclear) YAP in OGT TG compared to WT activity in OGA TG and OGT x OGA TG. YAP target genes were up regulated in OGT TG hearts but normal in OGA TG and OGT x OGA TG. OGA TG mice protected against TAC induced hypertrophy had decreased myocardial OGN levels and YAP/TEAD1 gene target expression. Increased O-GlcNAcylation in cardiac cells resulted in increased YAP/TEAD reporter activity and downstream signaling.

Conclusion: These data suggest a novel mechanism for YAP modulation in the heart through changes in O-GlcNAcylation.

ABSTRACT 160

Both Low and High Vitamin D Levels Increase Adverse Pregnancy Outcomes in Systemic Lupus Erythematosus

Nima Madanchi, Andrea Fava, Daniel W Goldman, Laurence S Magder, Michelle Petri

Purpose. The risk of adverse pregnancy outcomes is higher in systemic lupus erythematosus (SLE) compared to general population. This necessitates finding new targets and interventions. We evaluated the role of maternal 25-hydroxy vitamin D in adverse pregnancy outcomes in SLE.
Methods. We used the Hopkins Lupus Cohort data. Pregnancies without 25-hydroxy vitamin D levels during pregnancy or unknown pregnancy outcomes were excluded. 270 pregnancies were included. We used a time-to-event analysis to assess whether time-varying of 25-hydroxy vitamin D levels were associated with time to miscarriage or preterm delivery.
Results. We found a U-shape association between the maternal serum 25-hydroxy vitamin D level and the combined adverse pregnancy outcomes (P=0.0022), miscarriage (P=0.0045), and preterm delivery (P=0.0010). The lowest prevalence of adverse pregnancy outcomes was with 25-hydroxy vitamin D range of 40-60 ng/dL. The time-to-event model confirmed the same U-shaped association after adjustment for SLE disease activity and race, however, the increased risk among those with highest levels of vitamin D was not statistically significant due to the low number of cases.
Discussion and Conclusions. This is the first study on the association between vitamin D and adverse pregnancy outcomes in SLE. The association with high vitamin D and adverse pregnancy outcomes was not reported before. Our study was limited as although we found an association, a cause-and-effect relationship is not proven. Additionally, most of our patients were on vitamin D supplementation.
We recommend monitoring 25-hydroxy vitamin D levels during SLE pregnancies. The ideal 25-hydroxy vitamin D range was 40-59 ng/dL.

ABSTRACT 161

Analysis of pancreatic cancer risk variants using long read sequencing

Qiuhui Li, Carolina Montano, Jessica Hosea, Luke Morina, Bohan Ni, Moira McCormick, Justin Paschall, Beth Marosy, Michelle Kokosinski, Jessica Gearhart, Brian Craig, Alan Scott, David Mohr, Michelle Mawhinney, David McKean, Nicholas Roberts, Zhanmo Ni, Alexis Battle, Kimberly Doheny, Winston Timp, Michael Schatz, Alison Klein

Prevision preventive measurements such as BRCA1/2 genetic testing is of increasing popularity and have shown to be influential over clinical decision making. However, there is a mixture of direct and indirect effects, which made it difficult to predict the impact of BRCA1/2 testing on clinical resource utilization and patient's outcome. There is a need to better understand the impact of BRCA1/2 testing on actions toward clinical prevention of breast cancer (BRCA) and the effectiveness of those actions. We analyzed the MarketScan dataset, a retrospective real world insurance claim dataset, to discover the causal relationships between BRCA1/2 testing, patient menopausal status, family history, clinical actions, as well as eventual BRCA onset. To estimate the effect of BRCA1/2 testing on actions toward the clinical prevention of BRCA and BRCA outcome, we employed causal structure learning to for model specification and compared its performance to that specified with domain knowledge, clinical guidelines and expert opinion. We revealed small but positive effect of BRCA1/2 testing on chemoprevention and prophylactic surgery utilization with the data driven approach, some of which could not be captured by principled analysis or domain knowledge specified model. We also identified the causal effect of BRCA1/2 genetic testing on eventual breast cancer onset. The results were limited by the nature of insurance claim data; however, it provided a robust pipeline for analysis when domain knowledge is not sufficient to specify an unbiased model.

ABSTRACT 162

Understanding Impact of BRCA1/2 Testing on Healthcare Utilization and Clinical Outcome

Xuyang Li, Kevin Gorman, Ilya Shpitser, Carolyn Applegate, Casey Overby Taylor

Prevision preventive measurements such as BRCA1/2 genetic testing is of increasing popularity and have shown to be influential over clinical decision making. However, there is a mixture of direct and indirect effects, which made it difficult to predict the impact of BRCA1/2 testing on clinical resource utilization and patient's outcome. There is a need to better understand the impact of BRCA1/2 testing on actions toward clinical prevention of breast cancer (BRCA) and the effectiveness of those actions. We analyzed the MarketScan dataset, a retrospective real world insurance claim dataset, to discover the causal relationships between BRCA1/2 testing, patient menopausal status, family history, clinical actions, as well as eventual BRCA onset. To estimate the effect of BRCA1/2 testing on actions toward the clinical prevention of BRCA and BRCA outcome, we employed causal structure learning to for model specification and compared its performance to that specified with domain knowledge, clinical guidelines and expert opinion. We revealed small but positive effect of BRCA1/2 testing on chemoprevention and prophylactic surgery utilization with the data driven approach, some of which could not be captured by principled analysis or domain knowledge specified model. We also identified the causal effect of BRCA1/2 genetic testing on eventual breast cancer onset. The results were limited by the nature of insurance claim data; however, it provided a robust pipeline for analysis when domain knowledge is not sufficient to specify an unbiased model.

ABSTRACT 163

Human-centered assurance in technology-assisted surgery

Sue Min Cho, Robert Grupp, Catalina Gomez, Iris Gupta, Mehran Armand, Greg Osgood, Russell Taylor, Mathias Unberath

Image-guided navigation and surgical robotics are the next frontiers of minimally invasive surgery. 2D/3D registration is an essential, enabling algorithm for most of these systems, as it provides spatial alignment of preoperative data with intraoperative images. While these algorithms have been studied widely, there is a need for verification methods to enable human stakeholders to assess and either approve or reject registration results to ensure safe operation.

To address the verification problem from the perspective of human perception, we develop novel visualization paradigms and use a sampling method based on approximate posterior distribution to simulate registration offsets. We then conduct a user study (N = 22) to investigate how different visualization paradigms (Neutral, Attention-Guiding, Correspondence-Suggesting) affect human performance in evaluating simulated 2D/3D registration results.

All three visualization paradigms allow users to perform better than random guessing to differentiate between offsets of varying magnitude. The novel paradigms show better performance than the Neutral paradigm when using an absolute threshold to differentiate acceptable and unacceptable registrations (highest accuracy: Correspondence-Suggesting (65.1%), highest F1 score: Attention-Guiding (65.7%)), as well as when using a paradigm-specific threshold for the same discrimination (highest accuracy: Attention-Guiding (70.4%), highest F1 score: Corresponding-Suggesting (65.0%)).

This study demonstrates that visualization paradigms do affect the human-based assessment of 2D/3D registration errors. However, further exploration is needed to understand this effect better and develop more effective methods to assure accuracy. This research serves as a crucial step towards enhanced safety assurance and autonomy in technology-assisted image-guided surgery.

ABSTRACT 164

A prediction and optimization framework for improving hospital capacity management during demand surges

Felix Parker, Kimia Ghobadi

Effective management of hospital capacity is essential for improving quality of care for patients, controlling costs, and ensuring resiliency of the health care system. It is particularly critical during surge events, characterized by large, rapid increases in demand that strain hospital capacity, which have become increasingly frequent at many hospitals. These surges critically affect ED boarding, care quality and timeliness, and staff, impacting patient outcomes and hospital operations. The COVID-19 pandemic has exacerbated this issue, rendering traditional surge definitions and response plans obsolete. Frequent surge events have led to 'alarm fatigue', while existing response mechanisms are overwhelmed by the increased frequency and severity of these surges. Our research aims to establish a more effective framework for identifying significant surge events, predicting their occurrence, and enhancing strategies to either prevent or mitigate their effects. We developed a deep learning-based forecasting model to anticipate key hospital metrics indicative of a surge, assisting in timely and informed decision-making. Additionally, we designed optimization models for capacity management during surges, allowing for proactive and strategic responses.

In collaboration with the Johns Hopkins Hospital Capacity Command Center we implemented and refined our models to ensure they are practical and operationally relevant. We introduced interactive online dashboards to facilitate real-time decision-making, and are working to overhaul the current surge policy. Our work aims to make a significant step in surge management within healthcare settings, leveraging machine learning and optimization models to effectively identify, predict, and respond to surge events, ultimately enhancing patient care and hospital efficiency.

ABSTRACT 165

Lightweight Vision Transformer for Collision-Avoidance on Resource Constraint UGVs

Md Ragib Shaharear, Edward Humes, Tinoosh Mohsenin

In the realm of intelligent control systems for Unmanned Ground Vehicles (UGVs), autonomous collision avoidance is vital. This study introduces a lightweight Vision Transformer (ViT) designed for real-time hardware implementation, challenging traditional Convolutional Neural Networks (CNNs). Our optimized ViT achieves a high validation accuracy of 98.5\%, with 15.33 milliseconds latency and 65 frames per second throughput on Edge devices, fulfilling the real-time navigation demands of UGVs. The ViT model not only outperforms the CNN model in throughput by 1.86 times but also showcases enhanced energy efficiency, marking it as a highly suitable choice for energy-sensitive applications in autonomous navigation systems.

ABSTRACT 166

Environmental tobacco smoke (ETS) exposure concentrations at different venues and regions of the world: a literature review

Prasenjit Ghosh, Fred Norton, Christopher Jenkins, Kirsten Kohler, Ana M. Rule

Secondhand smoke (SHS) is a threat to the health of nonsmokers across the World. SHS constitutes a mixture of more than 4000 toxic, irritant and carcinogenic substances, out of which nicotine is employed as an environmental marker for SHS in air. In the global scale, approximately 40% of children and 34% of non-smoking adults are exposed to the SHS. SHS exposure has been found to cause respiratory development disorders in children and in adolescents they develop smoking tendencies. The sources of SHS exposure can be broadly classified into residential and non-residential (i.e. workplace, public place, vehicles). The objective of the current literature review is to extract data on nicotine concentrations reported in various SHS exposure assessment studies worldwide and categorize them based on type of household, type of venue and region of the world. Median SHS nicotine concentration in households in North America, South America, Europe and Asia are 0.13, 0.16, 0.01 to 1.92, and 0.09 µg/m3, respectively. Respective ranges of median SHS nicotine concentration measured in bars, restaurants, office buildings, schools, and hospitals are 0.1 to 5.95, 0.914 to 13.5, 0.05 to 1.2, 0.1 to 2.464, and 0.02 to 1.33 in several Asian, European and North and South American countries. The SHS exposure concentration ranges between smoking vs non-smoking households, as well as between the different types of venues will enable us to identify concrete cut-points to be able to categorize the different levels of smoking exposures and help inform policy interventions.

ABSTRACT 167

Design of a multicontrast laser endoscopy system for improving mucosal contrast

Taylor L. Bobrow, Suchapa Arayakarnkul, Saowanee Ngamruengphong, Nicholas J. Durr

Changes in vasculature, mucosal topography, and endogenous chromophore concentrations are important biomarkers in the progression of healthy gastrointestinal tissue to neoplasia. Imaging with engineered illumination has been widely explored for its sensitivity to these properties in ex vivo tissue, but in vivo investigation has been limited due to the incompatibility of these methods with flexible endoscopes and the regulatory and safety challenges associated with human testing. We present a Multicontrast Laser Endoscopy (MLE) system for imaging with spectral, directional, and coherent illumination in the clinical setting. Three applications of MLE are demonstrated: measuring hemodynamic differences in tissue with multispectral diffuse reflectance, estimating mucosal topography using photometric stereo, and quantifying blood perfusion using laser speckle contrast imaging. In addition to benchtop validation results, we present preliminary results from a first-in-human screening colonoscopy pilot study.