BU CTSI

12th Annual Translational Science Symposium

Advancing Translational Science Through Cutting-Edge Technology

Poster Presentations

1. AUDITORY-MOTOR ENTRAINMENT AS A DIAGNOSTIC GAIT BIOMARKER OF PARKINSONS DISEASES IN PEOPLE WITH MINIMAL GAIT DEFICIT

DHEEPAK ARUMUKHOM REVI[1,2], RUOXI WANG[1], FRANCHINO PORCIUNCULA[1], JENNA A. ZAJAC[1], TERRY ELLIS[1], AND LOUIS AWAD[1,2]

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2. THE ROLE OF SCAVENGER RECEPTORS AND VESICLE TRAFFICKING IN THE TRANS-ENDOTHELIAL MIGRATION OF BLOOD STEM CELLS

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3. LSD1 INHIBITION PROMOTES ANTI-TUMOR IMMUNITY IN HEAD AND NECK CANCER VIA THE IFNΓ-CXCL9-CXCR3 AXIS AND MHC-I UPREGULATION

BOSTON UNIVERSITY

BOSTON MEDICAL CENTER
EXCEPTIONAL CARE. WITHOUT EXCEPTION.

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Abstract

Introduction: Head and neck squamous cell carcinoma (HNSCC) have a poor prognosis, highlighting the need for new treatments. Lysine-specific demethylase 1 (LSD1), an epigenetic regulator, has shown promise in reducing tumor progression and increasing CD8+ T cell infiltration. This study explored how LSD1 inhibition promotes HNSCC-specific anti-tumor immunity, suggesting that it boosts CD8+ T cell responses by improving antigen presentation by dendritic cells (DCs) and changing cytokine levels and regulating MHC-I.

Methods: Using syngeneic, chronic carcinogen-induced, humanized, and *Kdm1a* knockout mouse models, along with *ex vivo* co-cultures and single-cell RNA sequencing, we examined the effects of the LSD1 inhibitor SP2509 on HNSCC. Flow cytometry, RT-qPCR, bulk and single-cell RNA sequencing, and chromatin immunoprecipitation (ChIP) assays were used to analyze immune cell numbers, gene expression, and histone modification patterns.

Results: LSD1 inhibition increased CD4+, CD8+ T cell, and DC numbers and activation in HNSCC models. It also increased immune response genes, IFNγ and CXCR3 in T cells, and CXCL9 in DCs, showing activation of the IFNγ-CXCL9-CXCR3 axis. scRNA-seq confirmed more DCs and higher *Batf3*, *Cxcl9* expression. SP2509 increased MHC class I expression in OSCC cells. Humanized models showed increased CD4+ and CD8+ T cell infiltration and activation. TCGA data showed an inverse correlation between *KDM1A* expression and key immune markers. LSD1 inhibition increased H3K4me2 and decreased H3K9me2 methylation at the *HLA-A* gene. Co-culture experiments showed that *KDM1A* knockout or SP2509 treatment increased IFNγ production by T cells, CXCL9 secretion by DCs, and MHC-I expression in epithelial cells. Blocking CXCL9 or CXCR3 reduced these effects.

Conclusion: These results show that LSD1 inhibition enhances anti-tumor immunity in HNSCC by improving DC-mediated antigen presentation via the IFNγ-CXCL9-CXR3 axis and increasing MHC-I expression. These mechanisms may lead to new immunotherapeutic strategies for HNSCC.

4. USING AI TO REDUCE WAITING TIMES FOR DERMATOLOGICAL CARE

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Abstract

Introduction: Dermatological AI (*DAI*) technologies (many of which are provided by third parties) may bring operational benefits and increase access to care. However, there is a lack of guidance on effectively integrating them into the clinical workflow.

Methods: This data-driven decision analytical study combines field data, mathematical models, and simulation to develop a cost-effective approach integrating *DAI* with in-person clinics. We partner with a large Health Maintenance Organization (HMO) with over two million members who launched a third-party *DAI* app for a limited patient group. The field data contains over 15,000 dermatological appointments in multiple clinics from the HMO. We track patients' waiting times for dermatology appointments, queue length with and without the *DAI* app, clinical throughput, system utilization, and total service cost, including *the DAI* app's third-party payments. We use the observed data to build and calibrate a mathematical model to optimize the HMO's dermatological workflow.

Results: Our model identifies an economical peak period waiting time threshold, recommending the HMO provide the *DAI* app for free to patients instead of making them wait weeks for in-person appointments. Clinics can achieve a 93% reduction in average waiting times with just 12% to 15% of patients using the *DAI*. Additionally, the *DAI* allows for the virtual pooling of patient queues, enhancing equitable access to care across clinics.

Conclusion: Excessive waiting times in dermatology cause significant patient dissatisfaction and may cause severe deterioration of time-sensitive issues. We propose using a Digital AI app for a small percentage of patients when waiting times for in-person appointments exceed a specific economic threshold set by the HMO. This approach reduces waiting times and enhances equitable access to care, only slightly increasing the HMO out-of-pocket costs.

5. PRIMARY MOUSE TRACHEAL BASAL CELLS TRANSPLANTED INTO CFTR-/- MICE RECONSTITUTE CFTR FUNCTION.

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Abstract

Introduction: Replenishing the airway stem cell compartment in cystic fibrosis (CF) via autologous basal cells with normal CFTR has the potential to treat CF lung disease regardless of underlying mutation. Towards the goal of developing cell therapy for CF, a preclinical in vivo proof of concept to test basal cell transplantation is necessary to understand the functional capacity of transplanted cells in their native niche. We previously demonstrated the capacity of primary and pluripotent stem cell derived basal cells to durably engraft in mice trachea after injury. Here, we demonstrate the successful transplantation of exogenous wild-type primary mouse basal cells into the tracheas of gut-corrected CFTR-/- mice that successfully restore CFTR expression and function.

Methods: Primary wild type UBC-GFP C57BL/6 mouse basal cells were isolated and expanded from fresh trachea and subsequently transplanted into heterozygous (n=4) and gut-corrected CFTR-/- (B6.129P2-KOCftrtm1Unc) (n=10) mice by oropharyngeal delivery following polidocanol conditioning of the recipient animals as we previously described. Recipient murine tracheae were analyzed after 6 weeks for engraftment efficiency, Cftr expression, and CFTR ion channel function.

Results: Donor-derived GFP was detected by epifluorescence in all transplant recipients with 2/4 heterozygous and 4/10 CFTR-/- mice showing significant (>=50%) coverage of endogenous epithelium by donor-derived GFP+ cells. Cftr mRNA was detected in all recipients; transplant recipients had increased Cftr transcript expression over non-transplanted CFTR-/- mice. Ussing chamber analysis of transplant recipients showed significant CFTR-dependent current in transplanted CFTR-/- over non-transplanted CFTR-/- mice and approaching levels of response seen in transplanted heterozygous animals.

Conclusion: Transplantation of primary murine basal cells with normal Cftr sequence can restore CFTR expression and function in the trachea of CFTR-/- mice.

6. DIRECT CONVERSION OF CENTENARIAN PBMCS AS AN IN VITRO MODEL OF AGING AND RESILIENCE

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Abstract

Introduction: The development of in vitro models of human aging and resilience to disease presents an attractive approach for the screening of longevity-related interventions. Neurodegeneration is a hallmark of aging-related decline, as dysfunction in neurons and supportive glial cells can trigger the onset of disease. Induced pluripotent stem cell (iPSC)-based systems have revolutionized our ability to model human disease through the generation of patient-specific cell types. However, reprogramming of somatic cells into iPSCs erases epigenetic marks, resetting cellular age and limiting utility in studying human aging. Therefore, it is

essential to develop age-equivalent human cellular models to study neurodegeneration and aging-related disease.

Methods: Here, we have isolated and banked peripheral blood mononuclear cells (PBMCs) from centenarians and their offspring. We have differentiated primary microglia from these blood blood samples to uncover mechanisms that promote resilience to aging-related neurodegeneration. In tandem, we have leveraged direct conversion – a process that preserves aging-related signatures – to generate cortical neurons via infection with a lentiviral cassette. Using these unique populations of cells, we have performed RNA sequencing and targeted methylation arrays to identify centenarian-specific aging signatures that may contribute resilience and longevity. We have also employed functional characterization of these cells via electrophysiology to validate adaptive modifications in longevity-specific cell types.

Results: Our initial findings demonstrate that cells produced by our protocols retain the unique aging signatures of the donor, presenting an opportunity to explore rejuvenative interventions aimed at decreasing biological age and improving functionality in vitro. These methods can be paired with iPSC-based systems to simultaneously study rejuvenation in age-equivalent neuronal cells as well as the maintenance of resilience in iPSC-derived neurons from the same individual. This model provides an improved understanding of the genetic and epigenetic signatures that promote resistance to aging-related disease in centenarians, aiding in the development of therapeutics at an individual level.

7. THE ASSOCIATION BETWEEN CAREGIVER-REPORTED CARE COORDINATION CHALLENGES AND PERCEIVED HEALTH STATUS: AN ANALYSIS OF THE 2023 NATIONAL SURVEY OF CHILDREN'S HEALTH

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Introduction: Care coordination is crucial for managing allergies, a common chronic condition affecting 5.2 million children in the United States. Food and environmental allergies require constant management. Caregivers often face challenges navigating healthcare systems, affecting their perception of their child's health. While care coordination is crucial for chronic conditions, its impact on children with allergies remains underexplored. We hypothesized that children lacking needed care coordination would have lower odds of excellent/very good health status compared to those receiving coordination services.

Study Question: How are caregiver-reported challenges in coordinating health care associated with the caregiver's perceived health status of children with allergies?

Methods: Using data from 2,626 children with allergies in the 2023 National Survey of Children's Health, we used SAS to analyze associations between caregiver-reported care coordination challenges and child health status through chi-square tests and multivariable logistic regression.

Results: Among children with allergies, 42.3% of caregivers reported needing care coordination, with 28.7% receiving it and 13.6% reporting unmet needs. Children lacking coordination had significantly lower odds of excellent/very good health compared to those receiving it (OR=0.365, 95% CI: 0.277-0.481), a

trend that persisted after adjusting for caregiver education and asthma status (aOR=0.382, 95% CI: 0.288-0.508).

Conclusions: Children who lacked needed care coordination showed significantly lower odds of excellent/very good health compared to those receiving coordination, with these associations remaining robust after adjusting for socioeconomic and demographic factors. While both care coordination and caregiver mental health independently showed significant associations with child health status, we found no significant evidence that these relationships were modified by age, family structure, or caregiver mental health.

8. SIALIDASES ASSOCIATED WITH BACTERIAL VAGINOSIS REMODEL THE SPERM GLYCOCALYX AND IMPAIR SPERM FUNCTION

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Abstract

Background: Bacterial vaginosis (BV), a dysbiosis of the vaginal microbiome, affects a third of women worldwide and is strongly associated with increased incidence of sexually transmitted infection (STI), preterm birth, and adverse outcomes for infants delivered full term. Bacterial vaginosis-associated bacteria, such as *G.vaginalis,* produce sialidase enzymes that degrade the vaginal mucosa by removing sialic acid moieties from cell surface proteins and mucins. This damage creates an inflammatory environment which likely contributes to adverse health outcomes. We hypothesized that BV-associated sialidases also damage sperm during their transit through the female reproductive tract (FRT) by remodeling sperm surface sialoglycoproteins, and that this may impact their survival in the FRT.

Methods: To investigate BV-associated damage to sperm, we produced recombinant sialidase derived from *G.vaginalis* (GvNanH2). Sperm were collected from healthy, reproductive aged men and treated with GvNanH2, or buffer only as a negative control. We confirmed the removal of sialic acids by measuring lectin staining with flow cytometry and surface charge via zeta potential. We investigated the functions of sperm in the FRT in the absence and presence of sialidase with a kinetic agglutination assay, a complement-mediated sperm immobilization assay, and a human cervical mucus penetration assay. Data were analyzed with a mixed-model and post-hoc Sidak testing to determine differences between sialidase-treated and untreated groups

Results: Here, we show that BV-derived sialidases remodel the sperm glycocalyx by removing cell surface sialic acids and reducing sperm surface charge by 10 mV. This resulted in increased sperm susceptibility to complement lysis (2-fold), agglutination (2-fold), and decreased sperm transit through cervical mucus (2.5 fold).

Conclusion: Our results demonstrate a mechanism by which sialidases in bacterial vaginosis may affect sperm survival and function and potentially contribute to the inflammatory environment associated with negative reproductive outcomes such as preterm birth, infertility, and adverse neonatal outcomes.

9. UNDERSTANDING THE MOLECULAR MECHANISMS OF EXCEPTIONAL LONGEVITY

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Abstract

Dynamic resiliency, or the ability to respond to and recover from stress, declines with age and results in increased frailty and susceptibility to disease. Individuals with exceptional longevity (EL) display remarkable resiliency and healthspan by delaying or escaping aging-related disease. However, the underlying mechanisms that drive resiliency remain unclear. Moreover, translational models of human resilience that allow for the functional testing of interventions are virtually non-existent. We leveraged access to EL and control cohorts to generate a first-of-its-kind bank of peripheral blood mononuclear cells and resultant induced pluripotent stem cells (iPSCs). We then combined associated phenotypic data with omics-based aging clocks to identify individuals at the extremes of resiliency and frailty. IPSC-derived neurons were generated from EL and non-EL subjects and exposed to mechanistically distinct stressors to stimulate responses aimed at restoring cellular function. Following stress, transcriptional and functional signatures of stress response and adaptation were observed. EL-derived cells significantly upregulated genes involved in protein quality control, integrity and functionality, and resistance to neurodegeneration. Live calcium imaging of produced neurons revealed that EL iPSC-derived neurons were able to maintain and restore functionality more efficiently at baseline and following insult. Additionally, mitochondrial dynamics observed through mitotracker staining showed a reduction in polarized mitochondria in EL neurons as compared to controls, suggesting a quieter metabolic load and mitochondrial landscape in EL cells. Collectively, our in vitro model of functional resilience synergizes omics-based discovery with the flexibility and translational impact of iPSC-based models. This model will allow for the cross validation of longevity-related discoveries and will be leveraged to identify biomarkers of resilience or decline at the level of the *individual* and to develop novel, personalized therapeutics for aging-related disease.

10. FINDING FERRITIN FOOTPRINTS IN 5-FLUOROURACIL-INDUCED CARDIOTOXICITY

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Abstract

Background: 5-fluorouracil (5-FU)-based therapies, used in the treatment of patients with gastrointestinal malignancies, are associated with an increased risk of atherosclerotic coronary artery disease (CAD), coronary artery vasospasm, and heart failure. Although the mechanism of 5-FU-induced cardiotoxicity remains unclear, *in vivo* studies have suggested that 5-FU triggers iron-dependent cell death by enhancing transferrin receptor expression. Moreover, rat models treated with 5-FU have higher iron concentrations in myocardial tissue compared to controls. Based on these molecular findings, we hypothesized that ferritin could be a clinical biomarker of cardiotoxicity among patients receiving 5-FU-based chemotherapy.

Methods: We performed a retrospective chart review on patients aged 18 and older receiving 5-FU-based intravenous chemotherapy at a Boston Medical Center from 6/1/22-6/1/24. Patients were identified via Clinical Data Warehouse query and data within 2 years of first 5-FU administration were collected by manual chart review. Potential cardiotoxicity was defined by the presence of any of the following: obstructive coronary artery disease detected on coronary angiography, new wall motion abnormalities on echocardiography, LVEF (left ventricular ejection fraction) decrease ≥10% from pre-treatment TTE, coronary vasospasm, pericardial effusion, or incident heart failure.

Results: Of the 93 patients receiving intravenous 5-FU at Boston Medical Center from 6/1/22-6/1/24, those with ferritin ≥100 ng/mL were nearly 5 times as likely to exhibit a potential manifestation of cardiotoxicity (adjusted odds ratio [aOR] 4.7, confidence interval [CI] 1.0-23.5) after adjusting for age and gender. Similarly, patients with ferritin ≥100 ng/mL were approximately 3 times as likely to experience treatment failure (aOR 3.2, CI 1.1-9.7).

Conclusion: Patients with ferritin ≥100 ng/mL appear to have an increased risk of cardiotoxicity and negative treatment outcomes. As a result, we encourage oncologists to routinely obtain iron studies among patients receiving 5-FU.

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11. AN IPSC-DERIVED HUMAN INTESTINAL ORGANOID MODEL OF EBOLA AND MARBURG INFECTION

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Abstract

Ebola virus (EBOV) and Marburg virus (MARV) are highly fatal filoviruses causing hemorrhagic fever with gastrointestinal (GI) dysfunction, including diarrhea, vomiting, and abdominal pain. Despite the development of vaccines and monoclonal antibodies for EBOV, no effective therapeutics exist for late-stage Ebola Virus Disease (EVD). Although much is kno12 wn about filovirus pathogenesis in animal models, the role of the intestine in late-stage EVD remains poorly understood. This dissertation addresses this gap by establishing a novel human intestinal organoid (HIO) model derived from human induced pluripotent stem cells (hiPSCs) to investigate the pathophysiology of filovirus-induced GI dysfunction.

The HIO model, capable of differentiating into both proximal (small intestine) and distal (colon) intestinal lineages, provides a physiologically relevant system for studying the impact of EBOV and MARV infections. Using single-cell RNA sequencing and CDX2-GFP reporter lines, we observed robust viral replication in CDX2+ enterocytes and significant epithelial damage. Transcriptomic analysis revealed altered cell junction pathways and ion transporters, critical in diarrhea pathogenesis. Notably, we identified differential immune responses: MARV infection induced strong upregulation of interferon alpha and gamma signaling, while EBOV suppressed these pathways, highlighting distinct immune modulation strategies.

Given the challenges of conducting filovirus research in Biosafety Level 4 (BSL-4) environments, this study also contributes to the development of experimental methodologies and imaging techniques that can be utilized within high-containment settings. The HIO model offers a valuable tool for studying filovirus-host interactions in a human-specific context, enabling safer and more accessible research into viral pathogenesis. By elucidating the disruption of the intestinal epithelial barrier and its impact on ion flux, our findings provide new insights into GI dysfunction in EVD and MVD, with implications for therapeutic development.

12. REVEALING IMMUNE SIGNATURES OF LASTING VACCINE-INDUCED IMMUNITY THROUGH SYSTEMS IMMUNOLOGY

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Abstract:

Vaccination saves millions of lives annually, yet infectious diseases remain a leading cause of death due to variability in vaccine-induced immune responses from genetic, environmental, and immunological factors. To address this challenge, we compared vaccines inducing durable immunity (e.g., Yellow Fever vaccine) with those needing annual administration due to transient immunity (e.g., seasonal influenza vaccine). We aimed to understand pre-vaccination immune profiles associated with establishing durable, protective immunity. Leveraging datasets from the Human Immunology Project Consortium (24 studies, six pathogens, 1,405 individuals), we analyzed immune signatures at cellular and molecular levels. Predictive modeling of early gene expression (7,262 genes) identified unique immunological pathways and pre-vaccination profiles differentiating durable from transient responses. Individuals with durable immunity exhibited higher baseline adaptive immune component activities: CD8 T cells, T helper cells, and B cells.

The IL-2, Wnt, and Notch signaling pathways were more active at baseline, suggesting a predisposition to long-lasting immunity. These pathways promote immune cell survival, differentiation, and immune memory maintenance, sustaining protective immunity beyond initial antigen exposure. Our findings reveal novel molecular drivers of durable immunity, paving the way for targeted vaccine designs that optimize long-term protection across diverse populations and pathogens.

13. DISSECTNG THE MECHANISTIC CONTRIBUTION OF THE COPD/PF GWAS GENE DSP TO ALVEOLAR EPITHELIAL CELL PHENOTYPES

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Abstract

Background: The geneAc variant rs2076295, idenAfied as the causal variant at the 6p24 locus by genome-wide associaAon studies in COPD and pulmonary fibrosis (PF), strongly affects the expression of the desmosomal protein desmoplakin (DSP) in lung but not other Assues. In PF, DSP expression is downregulated only in a subset of lung epithelial cells including alveolar type 2 cells (AT2s), a criAcal cell type in both pulmonary fibrosis and COPD. The goal of the project is to determine the mechanisms through which DSP regulates AT2 maturaAon and proliferaAon, and thereby contributes to the pathogenesis of COPD and PF, especially through the modulaAon of the Wnt/Tcf signaling pathway. We hypothesize that reduced expression of DSP in AT2 cells destabilizes cell juncAon complexes, releasing Armadillo proteins which then modulate signaling pathways including Wnt/Tcf signaling, leading to the regulaAon of AT2 maturaAon/proliferaAon.

Methods: Induced pluripotent stem cells (iPSCs) are differenAated into AT2s - called a]er iAT2s. DSP and its cell juncAon's partners (plakoglobin, p120 catenin and plakophilin 2) are knockeddown in iAT2 using CRISPRi, to study the effects on Wnt/Tcf signaling. Tcf and Kaiso (nuclear partner of p120 catenin) acAviAes can be measured by plasmids containing their binding sequence and luciferase.

Results: DSP knockdown (DSP-kd) of iAT2s results in the loss of desmosomes and disordered intermediate filaments in iAT2s with the dysregulaAon of adherens juncAons. DSP-kd also induces both proliferaAon and maturaAon of iAT2s, and modulaAon of Wnt/Tcf signaling (reducAon of Wnt targets expression and luciferase acAvity).

Conclusion: Wnt/Tcf signaling seems to play an important role in the biology of AT2, triggered by the dysregulaAon of cell juncAons. The use of iAT2 appears to be a promising human model to elucidate AT2 dysfuncAon and associated disease pathogenesis, to develop novel treatments for complex lung diseases including COPD and PF.

14. DEFINING THE FUNCTIONAL REQUIREMENTS OF THE FETAL BLOOD STEM CELL NICHE USING A NOVEL TAILLESS ZEBRAFISH MODEL

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15. MULTIMODAL MACHINE LEARNING FOR ASSESSMENT OF AMYLOID-BETA AND TAU PET POSITIVITY STATUS

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Abstract

Background: Alzheimer's disease diagnosis hinges on the detection of amyloid-beta plaques and neurofibrillary tau tangles, which can be achieved *in vivo* through positron emission tomography (PET). However, PET imaging is expensive and difficult to access outside of research settings. Here, we aimed to develop and validate a data-driven approach for identifying amyloid-beta and tau PET positive cases using multimodal standard of care data.

Methods: We developed a machine learning approach that can process multimodal features, including demographics, medical history, physical and neurological exam findings, neuropsychological assessments, APOE-e4 allele status, plasma and cerebrospinal fluid biomarkers, and neuroimaging, to identify persons who are likely to be positive on amyloid-beta and tau PET imaging. We processed data from 12,185 participants obtained from multiple cohorts and trained CatBoost classification models via supervised learning (training: N=10,352; testing: N=1833). For determining amyloid-beta positivity, a threshold of 24 centiloids was set based on predefined criteria. Similarly, tau PET positivity in the meta-temporal region was determined using a threshold of 1.40 standardized uptake value ratio, derived from a two-component Gaussian mixture model applied to the training dataset.

Results: On the external testing dataset, our CatBoost models achieved an area under the receiver operating characteristic curve of 0.85 for predicting amyloid-beta positivity and 0.85 for tau positivity. Additionally, our model demonstrated balanced accuracies of 0.74 and 0.76 for amyloid-beta and tau PET status predictions, respectively. Correlation analyses showed that model predicted probabilities were associated with amyloid ($r=0.60$, $p<0.001$) and tau ($\rho=0.45$,$p<0.001$) disease burden.

Conclusion: Our approach provides a cost-effective means by which to assess amyloid-beta and tau PET positivity without requiring participants to undergo expensive PET imaging. Such tools can be invaluable in real-world settings to increase efficiency in participant selection for drug trials that target amyloid-beta and tau pathologies, either individually or in combination.

16. DEVELOPMENT OF A UNIVERSAL CAR T CELL

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Abstract

Chimeric Antigen Receptor (CAR) T cell therapies are efficacious in treating blood cancers due to their capacity for targeted killing of cancer cells. However, costly and delicate methods to produce CAR T cells limit their wide-spread use. We seek to create an off-the-shelf CAR T cell using induced pluripotent stem cells (iCAR T cells). iCAR T cells will be immune privileged and express a facultative CAR, replacing T-cell receptor alpha beta (TCRab), to prevent host-vs-graft and graft-vs-host responses, respectively. Our goal is to engineer an immune privileged iPSC line with the capacity to differentiate into an iCAR T cells. Further, our immune privileged iPSCs could be applied to cellular engraftment procedures for other forms of disease.

Immune privilege gene edits will be performed on iPSCs using CRISPR/cas9 and then confirmed using PCR amplification, sequencing, karyotyping and flow cytometry. Both immune privileged and wildtype iPSCs will be differentiated into T cells using an established protocol. T cell phenotypes and expression of CAR and T cell markers will be analyzed using flow cytometry.

We successfully performed the gene knockouts and knockins granting immune privilege and CAR capabilities, confirmed after differentiating into hemogenic endothelium and lung basal cells. Yet, immune privileged iCAR Ts did not adequately express CARs, even when TCRab was not detected.

While the immune privilege was confirmed, majority of iCAR Ts showed TCR gamma delta expression preventing expression of the CAR under the TCR alpha promotor. Future studies investigations will seek to enhance the T cell differentiation protocol to better support T cells expressing TCR's with alpha and beta subunits.

17.HIGH-RESOLUTION CHARACTERIZATION OF AGE-SPECIFIC CHANGES IN HPV-NEGATIVE HNSCC

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Abstract

Introduction: It's been shown that elderly patients with head and neck squamous cell carcinomas (HNSCC) exhibit diminished survival outcomes compared to their younger counterparts. While the convergence of aging hallmarks and cancer hallmarks offers valuable insights, further work is needed to elucidate the age-specific mechanisms influencing HNSCC beyond the shared characteristics of these biological processes. To this end, we have assembled a hiqh-quality human single-cell RNA-sequencing HNSCC atlas profiling more than 230,000 cells across more than 50 patients, with ages ranging between 18 and 89, which provides a unique resource to investigate age-associated changes in the disease's heterogeneity.

Methods: To create the atlas, we integrated six publicly available single-cell RNAseq datasets from 54 HPV-negative patients. Cells were clustered, classified, and characterized by gene set enrichment analysis, both in the epithelial cell compartment and in the tumor microenvironment (TME). Differential expression and cell type proportion analyses were performed to identify genes and cell type compositional changes associated with age. Cell cell communication analysis was performed to identify interacting cell types and integrated with the differential expression analyses to identify interactions changing with age.

Results: We also identify distinct cell populations, such as vascular endothelial cells, that are more prevalent in older patients, as well as specific ligand-receptor pairs that are enriched with age

Conclusion: Further analyses are ongoing, and we plan to functionally validate the hypotheses generated, specifically the presence of differentially abundant cell populations, and age-specific ligand-receptor signaling events that lead to tumor growth.

18. SPATIAL PROFILING OF THE HEMATOPOIETIC STEM CELL NICHE IN THE HUMAN FETAL LIVER TO UNRAVEL THE EXTRINSIC SIGNALS CONTROLLING ENGRAFTMENT POTENTIAL

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Abstract

Hematopoietic stem cells (HSCs) can engraft and reconstitute a recipient's entire blood system. This remarkable transplantation potential underlies their widespread clinical use for the treatment of numerous hematological disorders. Unfortunately, ex vivo HSC culture and manipulation required for novel gene therapy and transplantation approaches, affect engraftment potential and thus the success of the transplant. To learn how to better support HSC functionality prior to transplantation, we previously profiled a population

of HSCs within the fetal liver (FL) that display enhanced engraftment potential and demonstrated that these cells can be identified via the functional marker Endothelial Protein C Receptor (EPCR). Combining immunofluorescence (IF) and spatial transcriptomics, we aim to further unravel the extrinsic signals present in the FL HSCs niche to understand how this microenvironment is specifically supportive to highly engraftable HSCs and how we can translate these signals to a clinically relevant transplantation setting. To this end, we sectioned FL tissue and optimized IF staining for EPCR, co-staining for CD45 (pan-hematopoietic marker) and CD133 (hematopoietic progenitor marker). Overlap of EPCR, CD45 and CD133 staining identified HSCs in proximity to endothelial cells (EPCR+CD45-) and other hematopoietic cells (CD45+). In line with this, spatial transcriptomic profiling of the FL (analyzed using Giotto Suite software) revealed key niche cell populations such as macrophages and endothelial cells, previously suggested to support HSCs in the FL. Having optimized the individual components, we will next combine these technologies and perform multiplex-IF staining and spatial transcriptomic analysis on a single FL section for a more in-depth assessment of HSC niche architecture and the signals supporting engraftment potential at this unique developmental time point. Findings generated from this novel profiling will drive advancements in ex vivo culture systems that better support stem cell functionality, ultimately improving the success of gene therapy and HSC transplantation approaches.

19. FLEXURAL PROPERTIES OF THREE CERAMIC FILLED RESIN COMPOSITE MATERIALS FABRICATED BY TWO 3D DENTAL PRINTERS

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Abstract

Background:

3D printing is widely used in dentistry for prosthetics, with several new permanent crown materials introduced. However, the strength data of different printed crown resins across printing systems remains unclear. Three resin materials PacDent Rodin Sculpture 1.0, Rodin Titan, and Rodin Sculpture 2.0 were evaluated for their flexural properties. Specimens included disc-shaped specimens (14×2mm²) for biaxial flexural strength testing (N=129) and rectangular bars (2×2×25mm³) for three-point bending tests (N=133). These specimens were fabricated using two 3D printers: Asiga MAX, and PacDent Rodin PRODLP Sculptur, with a layer thickness of 0.05 mm. Post-processing was performed: Ottoflash with nitrogen to polymerize the specimens and polish using a 15-micron diamond polishing disk to maintain consistent thickness. Specimens were divided into two groups: dry specimens (room temperature) and aged specimens (submerged in 37°C RO-water for three days). All specimens were soaked in 23°C water for one hour before testing. Flexural strength was tested with Instron 5566A. Biaxial flexural strength was calculated following ISO 6872 standards. Statistical analysis was performed via JMP Pro 17, using three-way ANOVA followed by Tukey's HSD test (α=0.05). Dry specimens exhibited significantly higher three-point flexural strength (139.09±1.84 MPa) and biaxial flexural strength (139.43±2.08 MPa) compared to wet conditions (99.77±1.86 MPa and 113.00±2.03 MPa, respectively). The Asiga printer demonstrated significantly higher three-point flexural strength (123.83±1.87 MPa) compared to the Rodin PRODLP

(115.03±1.84 MPa) but exhibited lower biaxial flexural strength (106.69±2.11 MPa) than the Rodin PRODLP (145.74±1.99 MPa). Rodin Sculpture 2.0 and Rodin Titan showed no significant difference in three-point and biaxial flexural strengths. Rodin Sculpture1.0 exhibited the lowest flexural strength. This study revealed that their flexural strength is significantly affected by storage conditions, the type of printer used, and the specific resin materials employed. This test of flexural strength may in part help predict the clinical performance of new crown materials.

20.EVALUATION OF MICROHARDNESS AFTER BIOMIMETIC REMINERALIZATION TREATMENT FOR TOOTH SURFACE

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Abstract

Introduction: The purpose of this research experiment was to determine the best possible tooth surface regrowth treatment after cycles of demineralization and remineralization. After the demineralization process to emulate artificial dental caries, the efficacy of an experimental biomimetic mineralization solution (BMS) was studied by evaluating the difference in hardness between enamel and dentin after treatment with BMS, which promotes the formation of harder hydroxyapatite (HAP) crystals on the tooth surface. If the hardness significantly increases after remineralization treatment, the biomimetic mineralization solution is considered effective.

Methods: The study explored two sets of samples: enamel and dentin. Extracted teeth (N=36) from oral surgery were disinfected, embedded in epoxy resin, and polished to expose the crown enamel or cervical dentin surfaces. Samples were subjected to lactic acid demineralization for 5 days to create artificial dental caries, then treated with experimental BMS to evaluate its remineralization effect. Vickers hardness was measured at baseline, after demineralization, and after remineralization using a Wilson VH 1202 microhardness tester. Four to eight Vickers indentations were made at each stage on each sample, and the averaged HV0.025 value was used for statistical analysis. Changes in surface microhardness values were compared using one-way ANOVA with JMP Pro 17 ($\alpha = 0.05$).

Results: With units of HV0.025, enamel and dentin had initial average hardness values of 361.58 ± 84.37 and 58.25 ± 5.53, respectively. After demineralization and BMS treatment, enamel hardness increased from 116.47 ± 61.65 to 207.50 ± 81.25, and dentin hardness rose from 24.73 ± 16.81 to 89.13 ± 27.54. These increases were statistically significant ($p < 0.001$).

Conclusion: BMS significantly improved microhardness values after demineralization. Future research aims to compare BMS treatment with commercial products for effectiveness in treating demineralized tooth surfaces.

21. PRIUS DECODES BRD4-MEDIATED CHROMATIN REMODELING DRIVING FIBROBLAST ACTIVATION

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Abstract

Excess fibroblast activation induced by stress contributes to cardiac dysfunction and pathological remodeling of the heart. However, the regulatory mechanism governing this process remains unclear. BRD4, a stress-responding protein, plays a widespread role in remodeling the chromatin landscape across various cell types. In *Cx3cr1*-expressing monocyte-derived macrophages, BRD4 induces transcriptional secretion of IL-1β to drive pathological fibroblast activation in heart failure. Pharmacological inhibition of BRD4 using the small molecule JQ1 has shown protective effects on stress-induced heart failure with improving cardiac function. However, the broad inhibition of BRD4 poses challenges due to its widespread binding sites across chromatin regions, highlighting the need for more precise cell-type-specific targeting strategies. We hypothesize that dynamic distal regions regulated by BRD4 in *Cx3cr1*-expressing macrophages are the primary driver of IL-1β production to induce fibroblast activation in response to stress. To address this, we developed a robust, cell-type-specific scoring system named PRIUS, Perturbed Regulation Indicator in cells Under Selection, to quantify stress-induced chromatin accessibility dynamic changes regulated by BRD4 in *Cx3cr1*-expressing macrophages. PRIUS integrates single-cell ATAC-seq and CUN&RUN datasets to quantify the regulatory potential of 23,520 BRD4-regulated distal regions in this subset of macrophages under stress. PRIUS successfully captures dynamic chromatin accessibility changes regulated by BRD4 in response to cardiac stress, as well as identifies BRD4-regulated enhancer regions. The top 100 genes regulated by those distal regions highlight their potential role in regulating the immune response in macrophages and contributing to cardiac fibrosis, further validating the capability of PRIUS. PRIUS informs novel, cell-type-specific therapeutic strategies for pharmacological intervening to reverse pathological cardiac remodeling at the cellular level.

22. UNMASKING JAK2^{V617F} MEGAKARYOCYTES IN BLOOD AND BONE MARROW: INSIGHTS FROM SINGLE-CELL RNA SEQUENCING

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Abstract

Introduction: The JAK2^{V617F} hyperactivating mutation in hematopoietic cells is associated with different forms of myeloproliferative neoplasms, but recently also found to increase propensity for cardio-pulmonary complications. Considering the existence of megakaryocytes in the lung and blood circulation, and our recent findings of increased megakaryocyte numbers in the lung and blood of mice carrying the human JAK2^{V617F} mutation in hematopoietic cells (Vav1-h JAK2^{V617F} transgenic mice), we hypothesized that the mutation reprograms these circulating cells towards a possibly more pathogenic phenotype.

Methods: We performed 10x Genomics Chromium single-cell RNA sequencing (scRNA-seq) of JAK2 ^{V617F} and matching (sex and age) control mouse blood and bone marrow megakaryocytes, which were isolated via flowcytometry cell sorting based on lineage markers. Samples included cells pooled from four JAK2 ^{V617F} and four control mice. Traditional preprocessing and subsequent downstream analysis methods were performed using Seurat in R to identify individual clustered cell types and differentially expressed genes across samples and clusters. The Database for Annotation, Visualization, and Integrated Discovery (DAVID) functional annotation tool was used to identify enriched pathways and functions specific to JAK2 ^{V617F} mutation.

Results: After removing experimental batch effects and individual variance, our clustering analysis of preprocessed scRNAseq data, using specific marker genes, identified megakaryocyte cells at various maturation stages in blood and bone marrow samples. This was based on expression of the following lineage markers: PF4, GPV, GPVI, MPL. Downstream differential gene expression analysis and functional enrichment analysis strikingly revealed upregulation of immunogenic, inflammatory, and thrombotic processes in the JAK2 ^{V617F} mutated megakaryocytes compared to WT controls.

Conclusions: Immunogenic, inflammatory, and thrombotic processes are enriched in circulating megakaryocytes with JAK2 V617F mutation. This is of particular interest concerning blood megakaryocytes, considering their potential to affect other tissues directly or through secreted factors.

23. TRANSPLANTATION OF HUMAN IPSC-DERIVED ENDOTHELIAL CELLS (IECS) IN ACUTE LIVER INJURY MOUSE MODELS AS A CELL THERAPY FOR IMPROVING LIVER REGENERATION

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Abstract

3 Key words: hiPSC-derived endothelial cells; mRNA-LNP; liver regeneration

Introduction: Liver sinusoidal endothelial cells (LSECs) are essential for liver homeostasis and function, playing pivotal roles in metabolism, immune response, and regeneration post-injury. Specifically, activation of the VEGFA/KDR axis in LSECs has been reported to support hepatocyte proliferation following

hepatectomy through paracrine signaling. Building on this, we hypothesize that promotion of human induced pluripotent stem cell (hiPSC) derived endothelial cell (iEC) engraftment by VEGFA will reconstitute the liver vasculature and mitigate liver disease.

Methods: We developed a modified protocol to generate iECs, expressing key markers CD31, CD144, KDR and LYVE1. To evaluate iEC engraftment and ability to reconstruct the sinusoid vasculature, luciferase-tagged iECs were transplanted into 2 acute liver injury mouse models using acetaminophen (APAP) and monocrotaline (MCT). Additionally, VEGFA via nucleoside modified mRNA in lipid nanoparticles were administered to investigate KDR activation in engrafted iECs in vivo.

Results: iEC engraftment with a low dose of VEGFA treatment was 1.78-fold higher in bioluminescence expression 7 days after APAP induced injury. Treatment with higher dose of VEGFA shows a 28.8-fold increase in signal from engrafted iECs 20 days after MCT induced injury. Immunofluorescence staining for human CD31 and mouse KDR confirm integration in host sinusoidal network.

Conclusions: VEGFA treatment enhances iEC survival and engraftment in acute liver injuries *in-vivo* shown by bioluminescence expression and histology. This study opens avenues for advanced therapeutic strategies in liver regeneration, leveraging the critical interplay between endothelial cells and hepatocytes

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24. PARTICULATE MATTER INDUCES AN INFLAMMATORY PHENOTYPE IN TYPE 2 ALVEOLAR EPITHELIAL CELLS

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Abstract

Introduction: Long-term exposure to air pollutants is significantly associated with emphysema. Particulate matter <2.5 um ($PM_{2.5}$), produced by combustion, can enter alveoli. Exposure to PM2.5 activates the release of proinflammatory factors, including the NLRP3 inflammasome and IL-1β. IL-1β levels are increased in emphysema patients and IL-1β has been shown to increase pulmonary inflammation through activation of alveolar macrophages. However, the mechanistic link between air pollution, IL-1β secretion, type 2 alveolar epithelial cell (AT2) function, and emphysema pathogenesis remains to be elucidated. Here, we utilize an induced pluripotent stem cell-derived AT2 model (iAT2) to understand how PM2.5 and IL-1β exposure impacts the function and transcriptional profile of AT2s.

Methods: iAT2s were exposed to PM2.5 or IL-1β +/- IL-1β receptor antagonist at a variety of doses and times. Gene expression was determined by qRT-PCR. Cytokine secretion was determined through Illuminex cytokine array. Proliferation was determined through EdU flow. NFkB activity was determined through transduction of a lentivirus containing a luciferase reporter.

Results: IL-1β treatment induced inflammatory gene expression, inflammatory cytokine secretion, and activation of the NFkB pathway in iAT2s. IL-1β treatment does not impact iAT2 proliferation. IL-1β receptor antagonism mitigates NFkB activation induced by IL-1β. PM2.5 exposure induced inflammatory and xenobiotic gene expression in iAT2s.

Conclusions: iAT2s exposed to IL-1β exhibit signs of inflammation and activation of the NFkB pathway. This inflammation can be partially mitigated through antagonism of the IL-1β receptor. PM2.5 exposure also appears to induce inflammation in iAT2s, through activation of proinflammatory genes. Further investigation is needed into the interactions of PM2.5 and IL-1β, impact on AT2 function, and methods of reducing inflammation caused by exposure to these factors.

25. INVESTIGATION OF VEGFA MRNA-LNP TO REDUCE THE LIVER DISEASE BURDEN VIA GENERATION OF HEALTHY HEPATOCYTES FROM CHOLANGIOCYTES

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Abstract

Introduction: Alpha-1 antitrypsin deficiency (AATD) is a genetic mutation resulting in the AAT protein misfolding into the Z-conformation, inducing hepatotoxicity. Currently, liver transplantation is the only cure for AATD-associated liver disease. However, due to the scarcity of available livers, patients often die before a transplant is available; thus, therapeutic alternatives to help these patients are in high demand. During severe liver injury when hepatocyte replication is compromised, biliary epithelial cells (BECs) are able to differentiate into hepatocytes to replace the lost tissue. The goal of this study is to utilize the innate BEC-driven liver repair mechanism to alleviate the AATD disease burden as a bridge therapy for patients awaiting transplant.

Methods: We generate a BEC lineage tracing mouse model using tdTomato reporter and CK19 Cre mice bred with the NSG-PIZ mouse which recapitulates AATD. Lineage tracing is induced by injections of tamoxifen, and then of AAV8-p21 to induce senescence in hepatocytes as seen in AATD patients. Afterwards, two injections of VEGFA mRNA-LNP are given to promote BEC-to-Hepatocyte conversion.

Results: Mice treated with the VEGFA mRNA LNP had significantly more tomato + area than control-treated groups, indicating that the stimulated BECs were converted into hepatocytes.

Conclusions: We show that VEGFA mRNA-LNP is a promising candidate for bridge therapy for AATD as it successfully induces BEC-to-Hepatocyte conversion. Future studies will test the synergic effect of multiple injections of VEGFA mRNA and determine the health of the newly generated hepatocytes with time to evaluate improvement of the liver disease.

26. STRATEGIES FOR THE RESCUE OF CELLULAR AND BEHAVIORAL DEFICITS IN A NEXMIF-DEPENDENT MOUSE MODEL OF AUTISM SPECTRUM DISORDER

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Abstract

We previously confirmed that loss of the X-linked gene *NEXMIF* results in Autism spectrum disorder (ASD). We have successfully established a *Nexmif* knockout (KO) mouse model which displays significant neuronal deficits and autism-like behaviors. We utilized postnatal reintroduction of NEXMIF and its downstream genes as a strategy for rescuing the impaired cellular and behavioral phenotypes in KO mice. We found that injection of a NEXMIF lentivirus into neonatal KO mouse brains rescues spine density and synaptic protein expression, reduces anxiety, and improves preference for social novelty and novel object recognition memory by adolescent ages. Additionally, reintroduction of *Filip1*, a top gene transcriptionally regulated by NEXMIF, rescues impaired dendritic outgrowth in cultured NEXMIF knockdown neurons, indicating that gene reintroduction may serve as a rescue strategy in loss of NEXMIF conditions.

Comparable to human female cases, our heterozygous (HET) female mouse model also shows autism-like behaviors and neuronal defects. Due to the female-specific process of X-chromosome inactivation, NEXMIF is expressed in a mosaic pattern in the HET brain: some neurons express wildtype (WT) NEXMIF, while other neurons lack NEXMIF (KO) and retain a silenced copy of WT *Nexmif* on the inactive X chromosome (Xi). We wondered whether the silenced WT *Nexmif* copy in KO neurons could potentially be expressed via X-chromosome reactivation. Indeed, we found that potent DNA methylation inhibitors can successfully reactivate WT *Nexmif* from the Xi in cultured WT and HET female mouse neurons. Moreover, injection of the inhibitors into the brains of neonatal WT and HET female mice was sufficient to increase cortical NEXMIF expression by P15. Lastly, the CRISPRa system can specifically upregulate NEXMIF expression in human female cells and in WT female mice. Overall, these findings lay the groundwork for further research aimed toward investigating the therapeutic potential of gene reintroduction and reactivation techniques in NEXMIF-dependent ASD.

27. VALIDATION OF A SICKLE CELL DISEASE-SPECIFIC IPSC PLATFORM AS A PRECLINICAL SCREENING TOOL

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Abstract

Sickle cell disease (SCD) affects over 100,000 people in the US and ~8 million worldwide. While SCD patients all carry the same point mutation in their (adult) beta globin gene, their genetic background to some extent dictates disease severity and response to treatment. Current treatments for SCD aim to re-activate fetal hemoglobin (HbF) expression to offset the defect in adult hemoglobin, which results in anemia, vaso-occlusive crises and a range of downstream complications. Here, we demonstrate the potential of a SCD-specific iPSC platform to assess HbF induction potential of various therapeutics across the diverse SCD patient population. We specified SCD patient derived-iPSCs towards the erythroid lineage following our previously established erythroid differentiation protocol and dosed the cells with inducers of HbF such as Hydroxyurea (HU) and RN-1, mimicking the main therapeutic strategy for SCD. Flow cytometric assessment of HbF induction across five SCD lines and one control line, showed a differential response to HbF inducing agents both within and across SCD patient backgrounds, in line with what is seen in the SCD patient population. Moreover, patient-specific iPSC-derived erythroid cells were able to recapitulate a treatment response corresponding to clinical outcomes in individual SCD patients and suggested an alternative treatment for a patient failing to respond to Hydroxyurea. These results demonstrate that HbF induction can be modeled in iPSC-derived erythroid cells using a variety of therapeutics and across different genetic backgrounds. Importantly, they underline the potential of our SCD-specific iPSC platform as a pre-clinical screening tool that factors in genetic diversity, and thus its promise for advancing drug development pipelines.

28. PREDICTING COGNITIVE IMPAIRMENT USING NOVEL FUNCTIONAL FEATURES OF SPATIAL PROXIMITY AND CIRCULARITY IN THE DIGITAL CLOCK DRAWING TEST

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29. INNER RETINAL CELL LAYER THICKNESS IS ASSOCIATED WITH GLIAL FIBRILLARY ACIDIC PROTEIN IN PLASMA

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Abstract

Introduction: Retinal cell layer thickness has been associated with neurocognitive conditions such as Alzheimer's Disease (AD). We evaluated the association between retinal cell layer thickness and glial acidic fibrillary protein (GFAP), a neuropathologic protein associated with AD, in plasma, vitreous humor, aqueous humor, and tears.

Methods: This cross-sectional study included 50 patients who underwent vitrectomy and spectral domain optical coherence tomography imaging of the macula. Automated retinal layer segmentation was performed by the Heidelberg, Spectralis software. The association between inner retinal cell layer thicknesses and GFAP were measured by ELISA and evaluated with linear regression adjusted for age, race, gender, diabetic retinopathy, glaucoma, and apolipoprotein e4 allele genotype. P-values less than 0.05 within a false discovery rate (FDR) of 10% were considered significant.

Results: Higher plasma GFAP levels were significantly associated with a thinner nerve fiber layer at the superior outer macula (SOM) (p=0.031), nasal OM (NOM) (p=0.009), and inferior OM (IOM) (p=0.004) as well as a thinner ganglion cell layer at the superior inner macula (SIM) (p=0.007), NOM (p=0.022), and inferior IM (IIM) (p=0.015), temporal IM (TIM) (p=0.036), and temporal OM (TOM) (p=0.048). Higher plasma GFAP levels were also associated with thinner inner plexiform layer at the nasal IM (p=0.039), NOM (p=0.044), IIM (p<0.001), TIM (p=0.013), and TOM (p=0.036). Furthermore, higher plasma GFAP was significantly associated with a thinner total inner retinal cell layer thickness for all subfields (p<0.05 and FDR <10%) except IOM and TOM. GFAP levels in eye fluids were not significantly associated with cell layer thickness.

Conclusions: Higher plasma GFAP levels were associated with thinner inner cell layers, indicating that retinal neurodegeneration may be associated with AD protein biomarkers in plasma. Future studies can investigate whether retinal imaging markers combined with plasma proteins can serve as tools for screening and risk assessment in neurodegenerative disorders.

Table. Multivariate regression analysis results for the association between GFAP in plasma and inner retinal cell layer thickness at ETDRS OCT subfields adjusted for age, race, gender, diabetic retinopathy, glaucoma, and apolipoprotein e4 allele genotype. Significant associations have a p-value < 0.05 and FDR

30. TRANSITIONS FROM INJECTION TO RESPIRATORY OPIOID USE IN THE FENTANYL ERA

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Abstract

Introduction: The opioid crisis has shifted from prescription opioids to heroin and synthetic opioids, with smoking emerging as a prevalent route linked to overdose deaths. While once considered safer than injection, smoking's efficacy as a harm reduction strategy amid the fentanyl surge is unclear. This study aims to (1) describe opioid administration trajectories using Sankey plots, hypothesizing significant shifts from injection to smoking or sniffing, and (2) characterize individuals making these changes, hypothesizing that younger users and those with overdose experiences are more likely to switch to non-injection routes.

Methods: We performed a secondary analysis using Data from the REBOOT trial. participants with at least three study interactions were analyzed. Independent variables included overdose experiences during the study, recent witnessed overdoses, and age. The dependent variable was transitioning from injection to exclusively respiratory routes. Descriptive statistics summarized baseline characteristics; bivariate analyses (chi-square tests, t-tests) compared switchers versus non-switchers.

Results: A significant proportion of participants in both sites transitioned from injection to respiratory absorption of opioids, with nasal use more common in Boston and smoking more common in San Francisco. Younger participants and those who witnessed overdoses were significantly likely to switch to respiratory routes. Sankey plots illustrated dynamic transitions, with few reverting to injections.

Conclusions: These findings reveal evolving opioid use behaviors with implications for harm reduction. The link between overdose experiences and transitions to respiratory routes highlights the need for targeted interventions. Future research should examine the long-term health effects of smoking opioids and refine harm reduction strategies to address changing drug use patterns.

31. ENABLING BIOMEDICAL INSIGHTS WITH SCALABLE SPATIAL OMICS ANALYSIS

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32. MACHINE LEARNING IDENTIFIES SEVEN PNEUMONIA SUB-PHENOTYPES BASED ON PULMONARY HISTOPATHOLOGY

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33. MU OPIOID RECEPTOR ACTIVATION ENHANCES HIV-1 INFECTION AND VIRUS-INDUCED INFLAMMATORY RESPONSES IN MICROGLIA

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Abstract

People living with HIV-1 (PWH) and chronically using opioids have elevated risks of developing HIV-associated neurological disorders (HAND). HAND is a spectrum of neurocognitive deficits often marked by chronic inflammation. Microglia, innate immune cells in the brain, are the principal HIV-1 reservoir in the CNS and regulators of neuroinflammation. Our group has previously shown that HIV-1 infection of induced pluripotent stem cell-derived microglia (iMGs) and expression of viral intron-containing RNA (icRNA) triggers inflammatory responses. Microglia express μ opioid receptor, MOR, though immunomodulatory effects of opioids on HIV-1-infected microglia are unclear. Thus, we evaluated MOR activation effects on HIV-1 infection in MOR-expressing iMGs and MOR-deficient macrophages. Cells were pretreated with morphine before HIV-1 infection, and effects of MOR activation on virus replication and virus-induced inflammatory responses were determined by digital droplet PCR (ddPCR), confocal microscopy, flow cytometry, and ELISA. Morphine pretreatment enhanced reverse transcription (RT), integration, icRNA transcription, and p24Gag secretion in iMGs, but not macrophages, which was blocked by treatment with naloxone, a MOR antagonist. Furthermore, exogenous expression of MOR in macrophages rescued morphine-mediated enhancement of HIV-1 RT, proviral establishment, and icRNA expression, suggesting that MOR signaling intersects multiple steps of the virus life cycle. Importantly, morphine treatment enhanced HIV-1 icRNA-induced IP-10 secretion in MOR+ cells, which was suppressed by naloxone and a

PI3K inhibitor, wortmannin. Previous studies suggest that MOR signaling and HIV-1 infection can independently activate the PI3K-Akt signaling pathway. In support of this premise, MOR activation by morphine during HIV-1 infection induced Akt phosphorylation, which was blocked by naloxone and wortmannin, indicating that MOR signaling and HIV-1 synergistically activate the PI3K-Akt signaling pathway in microglia to exacerbate virus-induced inflammatory responses. These findings suggest that therapeutics antagonizing MOR activation or PI3K-Akt pathway may suppress HIV-1-associated neuroinflammation and reduce the incidence of HAND in PWH using opioids.

34. MULTI-OMIC ANALYSIS OF PLACENTA-DRIVEN PREECLAMPTIC DEVELOPMENTAL LUNG INJURY

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Abstract

Introduction: The lung disease of bronchopulmonary dysplasia (BPD) continues to impact the health of preterm infants worldwide despite decades of research. Preeclampsia (PE), a placental-driven pregnancy disorder, has a strong clinical association with BPD risk, but the mechanisms driving this association have not been well defined. We hypothesize that preeclampsia causes a unique type of developmental lung injury that predisposes infants to an increased risk of BPD. Objective: Using spatial transcriptomics (Sp-Tr) and proteomics, we conducted a pilot study examining primary human PE placental tissues to identify gene and protein signaling changes with connections to lung developmental pathways.

Methods: For Sp-Tr analysis, placental tissues were collected from pregnant patients with PE or gestational hypertension (GHTN) and evaluated using the 10x Genomics Visium platform. For proteomic analysis, conditioned media was collected from explant cultures of placental tissues from pregnant patients with preterm labor (PTL) or PE (n=3 each).

Results: In our Sp-Tr studies, we identified unique placental cellular niches with gene expression changes related to lung injury including proinflammatory signaling, neutrophil recruitment, and iron regulation. Proteomic analysis of placental secreted proteins also identified over 2500 secreted proteins with significant expression changes in PE vs PTL. Among these were a unique upregulation of soluble endoglin (sENG), a decoy receptor for TGF beta. TGF beta plays a prominent role in lung development and has been implicated in the pathogenesis of BPD.

Conclusions: Multi-omic analysis of human preeclamptic placental tissues is an informative novel approach to evaluate PE-associated changes in placental signaling that have the potential to impact the pulmonary developmental niche. This pilot analysis provides an important foundation for future work in expanded tissue cohorts and mechanistic studies to further define the mechanisms of preeclamptic developmental lung injury.

35. MULTIMODAL SINGLE CELL PROFILING REVEALS SPATIAL IMMUNE DYSREGULATION IN LYMPH NODES OF NON-SMALL CELL LUNG CANCER PATIENTS

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Abstract

Introduction: Tumor-draining lymph nodes (LNs) play a critical role in non-small cell lung cancer (NSCLC) progression, yet the immune microenvironmental changes occurring prior to metastasis remain poorly understood. We hypothesize that tumor-draining LNs in NSCLC undergo significant immune microenvironment changes, including the enrichment of immunosuppressive populations and the disruption of B cell follicular structures, mediated by distinct spatial interactions that create pre-metastatic niches conducive to tumor immune evasion and progression.

Methods: Tissue specimens from 10 NSCLC patients were analyzed using Cellular Indexing of Transcriptomes and Epitopes (CITE-seq) and imaging mass cytometry (IMC). Immune populations were identified, and spatial interactions were assessed in low-stage and high-stage LNs. Transcriptomic and proteomic profiling was used to characterize immune niches and structural changes in B cell follicles.

Results: High-stage LNs exhibited enrichment of mature regulatory dendritic cells (mregDCs), plasmacytoid dendritic cells (pDCs), exhausted CD8+ T cells, and CD4+ regulatory T cells (Tregs), particularly in N1 nodes. Spatial analysis revealed co-localization of mregDCs with Tregs and exhausted CD8+ T cells, forming immunosuppressive niches unique to high-stage LNs. B cell follicles in low-stage LNs were well-defined and surrounded by fibroblasts, while high-stage LNs showed disrupted, diffused B cell follicles interwoven with TIM3+ macrophages. These disruptions correlated with altered immune interactions, suggesting that TIM3+ macrophages contribute to the disorganization of B cell follicles. Multimodal profiling also revealed discrepancies between transcriptomic and proteomic markers for immune cell exhaustion, underscoring the importance of integrating spatial and molecular analyses.

Conclusions: This study identifies immune microenvironmental changes in high-stage LNs of NSCLC, including the formation of immunosuppressive niches and the disruption of B cell follicular structures in high-stage disease. These findings support our hypothesis and highlight potential biomarkers and therapeutic targets for mitigating immune evasion and metastatic progression in NSCLC.

36. SPATIAL PROFILING OF THE PANCREATIC NEUROENDOCRINE TUMOR MICROENVIRONMENT

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Abstract

Introduction: There is an urgent need to identify novel biomarkers that can accurately predict prognosis and potential response to systemic and targeted therapies for patients with pancreatic neuroendocrine tumors (PanNETs), a tumor type rapidly rising in prevalence. Recent studies have revealed prognostic biomarkers but limited to cancer cells and do not provide a systematic assessment of information encoded within the intact tumor microenvironment (TME), as well as the spatial organization of the TME. Thus, to uncover the underlying processes driving tumor initiation and progression in PanNETs, we used a combination of novel spatial technologies approaches to correlate tumor and TME spatial profiles with established biomarkers to characterize unique PanNET subtypes.

Methods: Two tissue microarrays (TMAs) were constructed representing 62 archival PanNETs with accompanying clinical data. Lunaphore COMET and Visium Cytassist, together with Immunohistochemistry (IHC) on clinical markers were performed on adjacent sections of the TMA. Next, integrative analysis was performed using Giotto Suite. In addition, unbiased histomorphology features and immunofluorescence features were captured and integrated with HIPT and Cellpose, to integrate for niche identification.

Results: Overall, Visium captured more than 80 cores whereas Lunaphore captured over 100 cores out of these samples, together with IHC images. With Computational image registration, we created a multi-modal and multi-scale dataset. We next performed unsupervised clustering and identified clusters correlated with different spatial organizations and clinical information. Collagen genes were identified significantly enriched in alternative lengthening of telomeres(ALT+)cases, multiple spatial co-expression patterns related to cell adhesion process were identified.

Conclusions: This work will delineate the spatial characteristics of the tumor and TME and, by coupling new biological insights with biomarker discovery, we envision further improving prognosis and uncovering potential therapeutic targets for the treatment of patients with PanNETs.

37. A MODIFIED DIETARY APPROACHES TO STOP HYPERTENSION (MDASH) INDEX IS ASSOCIATED WITH REDUCED RISKS OF SELECTED CARDIOMETABOLIC OUTCOMES

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Abstract

Introduction: We developed a modified Dietary Approaches to Stop Hypertension (mDASH) index that includes total dairy irrespective of fat content and total vegetables (including potatoes) unlike some earlier DASH indexes. This prospective study examined whether mDASH provides an equally strong reduction in hypertension (HTN), atherosclerotic cardiovascular disease (ASCVD), and non-alcoholic fatty liver disease (NAFLD) compared with earlier low-fat DASH indexes.

Methods: Participants with valid dietary data and no prevalent disease for each outcome were included (n=1714 for HTN; n=2700 for ASCVD; n=1406 for NAFLD analyses). In addition to mDASH, DASH Index I (Fung) and DASH Index II (Günther) were calculated. Cox regression models were used to estimate hazard ratios (HR) for HTN and ASCVD, while modified Poisson regression was used for NAFLD risk ratios, adjusting for demographic, lifestyle, and medical history.

Results: There were 712 HTN, 597 ASCVD, and 268 NAFLD cases over 11, 24.5, and 6 years (median), respectively. High adherence to mDASH (quintile 5 vs. 1) was associated with a larger reduction in HTN risk (HR: 0.67; 95% CI: 0.51–0.89) than DASH Index I (HR:0.74; 95% CI:0.58–0.94) and DASH Index II (HR:0.84; 95% CI:0.68–1.04). Score quintile 5 (vs. quintile 1) on mDASH and DASH Index I, but not DASH Index II, were associated with statistically significant 29-30% lower ASCVD risks. For NAFLD, higher (vs. lower) adherence to mDASH and DASH Index II was associated with statistically significant 29% lower risks, whereas DASH Index I was not.

Conclusions: The mDASH eating pattern that encourages higher consumption of total fruits and vegetables and total dairy, irrespective of fat content, was equally or more effective in reducing the risk of HTN, ASCVD, and NAFLD than traditional DASH indexes. These findings support the inclusion of nutrient-rich foods like full-fat dairy in the DASH diet for improved cardiometabolic health.