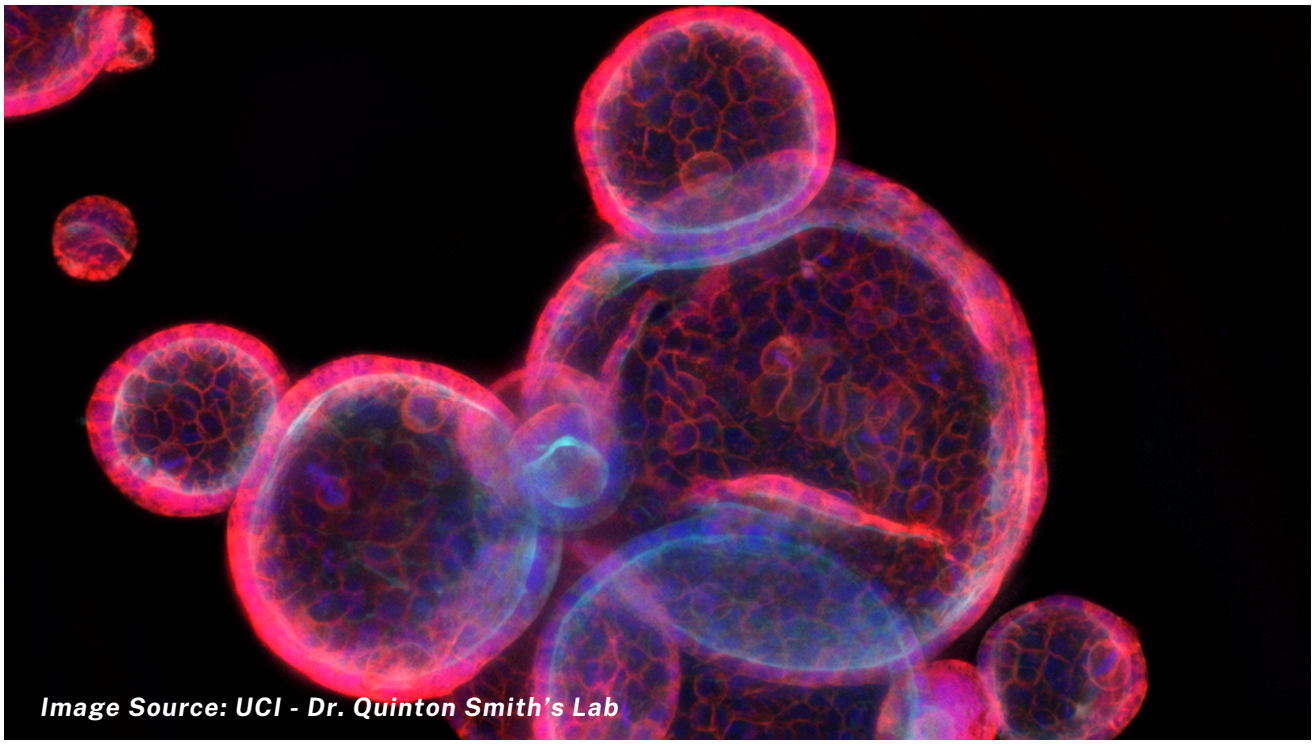
UCI Sue & Bill Gross Stem Cell Research Center

12TH ANNUAL STEM CELL SYMPOSIUM



UCI Stem Cell Research Center
Sue & Bill Gross Hall
February 12th, 2025
9:00 AM - 7:00 PM

UCI Sue & Bill Gross Stem Cell Research Center

Symposium Agenda

Registration & Breakfast - *Boardroom* **8:30 - 9:10 AM**

Introduction by Aileen Anderson, Ph.D.. **9:10 - 9:20 AM**

Session 1: Immune System & Blood Stem Cells - Moderated by Minji Byun, Ph.D.

Andras Nagy, M.D., Ph.D. - University of Toronto **9:20 - 10 AM**
"Safe, Immune-Cloaked, Allogeneic Cell Transplants for Long-Term Delivery of Therapeutic Biologics in Disease Treatment

Matthew Inlay, Ph.D. - UC Irvine **10 - 10:40 AM**
"Ex Vivo Graft Conditioning for Reduction in Graft-Versus-Host Disease Upon Allogeneic Hematopoietic Stem Cell Transplantation"

Naomi Lomeli, Ph.D. - UC Irvine **10:40 - 11 AM**
"*Development of Translational Models of Ovarian Cancer-Associated Cognitive Impairments and Chemotherapy-Induced Peripheral Neuropathy*"

Panel: Stem Cell Avenues to Translation **11 - 11:45 AM**
Daniela Bota, M.D., Ph.D., Leigh Turner, Ph.D., Alex Minella, M.D., Alanna Gannon. Ph.D. | *Moderated by Peter Donovan Ph.D.*

Lunch Buffet - *Boardroom* **11:45 - 1 PM**

Session 2: Cardiovascular Models & Bioengineered Systems - Moderated by Asuka Eguchi, Ph.D.

Joseph Wu, M.D., Ph.D. - Stanford University **1 - 1:40 PM**
"Stem Cells & Genomics: From Precision Medicine to Clinical Trials in Dish"

Sujeung Lim - UC Irvine **1:40 - 2 PM**
"Complementary Peptide Coassemblies for Driving the Structural Order of Thermochromic and Phototransducer Nanomaterials"

Quinton Smith, Ph.D. - UC Irvine **2 - 2:40 PM**
"Engineering Vascularized Organoids"

UCI Sue & Bill Gross Stem Cell Research Center

Symposium Agenda

Afternoon Break - - *Boardroom* **2:40 - 3 PM**

Session 3: Neuromuscular Disease & Aging - Moderated by Matthew Rose, M.D., Ph.D

Usha Nekanti, Ph.D. - UC Irvine **3 - 3:20 PM**
"Restoration of Cortico-Muscular Connectivity by Biomaterials Scaffolds and Neural Stem Cells After Spinal Cord Injury"

Albert La Spada, M.D., Ph.D. - UC Irvine **3:20 - 4 PM**
"Delineating Novel Pathways of Motor Neuron Demise in Amyotrophic Lateral Sclerosis"

Thomas Rando, M.D., Ph.D. - UC Los Angeles **4 - 4:40 PM**
"Stem Cell Quiescence: A Microcosm of Evolutionary Trade-Offs"

Closing Remarks by Aileen Anderson, Ph.D. **4:40 - 4:50 PM**

Poster Session **5 - 6:30 PM**

Roaming Dinner & Bar - *Boardroom & 4th Main Enterence*

Awards Ceremony **6:30 - 7 PM**

Clinical Research Coordinator Training Program

GMP Facility Operations Training Program

CIRM Training Grant

Alpha Clinic Clinical Trial Investigator Training Program

Student Poster Session Awards & Oral Presenters Recognition

Non-UCI Affiliated Attendees:
Park-By-Plate Link

Please submit your car information to avoid ticketing

Session 1: Immune System and Blood Stem Cells

INTRODUCING OUR SPEAKERS

Andras Nagy, MD, PhD - University of Toronto

Dr. Andras Nagy is a Shawn Kimel Senior Scientist at the Lunenfeld-Tanenbaum Research Institute, Sinai Health System, and a Professor in the Department of Obstetrics & Gynecology and the Institute of Medical Science at the University of Toronto. He holds a Tier I Canada Research Chair in Stem Cells and Regeneration and is recognized as a Fellow of the Royal Society of Canada in the Life Sciences Division of the Academy of Science. Dr. Nagy is a Foreign Member of the Hungarian Academy of Science, an Honorary Professor at the University of Helsinki, and holds a Distinguished Visiting Professor at Hong Kong University. His extensive contributions to stem cell research and regeneration have established him as a leading figure in the scientific community.

Matthew Inlay, PhD - UCI Irvine

Matthew Inlay received his Bachelor's degree from UC Berkeley in 1997, then moved to UC San Diego for graduate school. There he joined the Yang Xu lab and did his thesis work in Immunology on the regulation of V(D)J recombination by the immunoglobulin kappa light chain enhancers. Upon receiving his Ph.D. in Biology in 2003, he moved back to Northern California in 2005 to join Irv Weissman's lab at Stanford University for his post-doc. There he studied lymphocyte development, hematopoietic stem cell biology, and subsequently embryonic hematopoiesis. In 2013, Matt returned to Southern California to join the Sue and Bill Gross Stem Cell Research Center at UC Irvine as an assistant professor, where he now resides with his wife and son.

Naomi Lomeli, PhD - UCI, Bota Lab

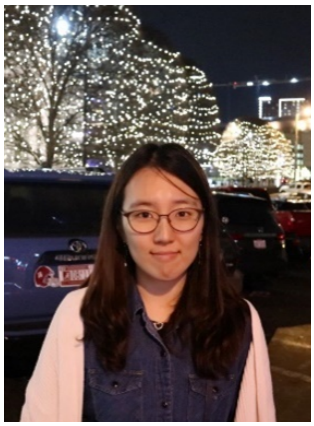
Naomi Lomeli received her PhD in Experimental Pathology and Laboratory Medicine at the University of California, Irvine. Naomi's research examines mechanisms of cisplatin-induced neurotoxicity in vitro in neural stem cells, hippocampal neurons, and in vivo ovarian cancer rodent models. She is interested in investigating translational therapeutic strategies for preventing CRCI and CIPN to improve the quality of life of cancer survivors.

Session 2: Cardiovascular Models & Bioengineered Systems

INTRODUCING OUR SPEAKERS

Joseph Wu, MD, PhD - Stanford University

Joseph C. Wu, MD, PhD is Director of Stanford Cardiovascular Institute and Simon H. Stertzer, MD, Professor of Medicine and Radiology at Stanford University. Dr. Wu received his MD from Yale University and PhD (Molecular & Medical Pharmacology) at University of California, Los Angeles. He is board certified in cardiovascular medicine. His lab works on cardiovascular genomics and induced pluripotent stem cells (iPSCs). The main goals are to (i) understand basic disease mechanisms, (ii) accelerate drug discovery via “clinical trial in a dish” concept, and (iii) implement precision medicine for patients. Dr. Wu has published >600 manuscripts with H-index of 138 on Google scholar. He is listed as top 0.1% of highly cited researchers by Web of Science for past 6 years (2018-2023).



Sujeung Lim - UCI, Ardoña Lab

Sujeung Lim is a Ph.D. candidate of Chemical and Biomolecular Engineering at UC Irvine. She completed her Bachelor of Science in Chemical Engineering at California State University, Long Beach, and her Master of Science in Pharmaceutical Sciences at USC. She uses a new biomaterials-based platform to use light to wirelessly pace CM functionality and help address the longstanding challenge in hiPSC-CM immaturity.

Quinton Smith. PhD - UC Irvine

Quinton Smith is an Assistant Professor in the chemical and biomolecular engineering department at the University of California, Irvine, and holds joint appointments in biomedical engineering and materials science and engineering. He received his bachelor’s degree in chemical engineering from the University of New Mexico in 2011 and his Ph.D. in chemical and biomolecular engineering from Johns Hopkins University in 2017. As a graduate student, he was mentored by Dr. Sharon Gerecht and used engineering approaches to investigate the role of mechanical forces on stem cell differentiation towards vascular populations. He was named a Siebel Scholar as a graduate student, and the National Science Foundation Graduate Research Fellowship Program and a National Institutes of Health F31 fellowship supported his work. As a Howard Hughes Medical Institute Hanna Gray Postdoctoral fellow under the mentorship of Dr. Sangeeta Bhatia at the Massachusetts Institute of Technology, Dr. Smith focused on leveraging microfluidic and organoid technology to model liver development and morphogenic processes. Dr. Smith was recently named a PEW Biomedical Scholar, which supports his research at UCI using stem cell-based model systems to study health disparities in the context of metabolic and cardiovascular disorders.

Session 3: Neuromuscular Disease & Aging

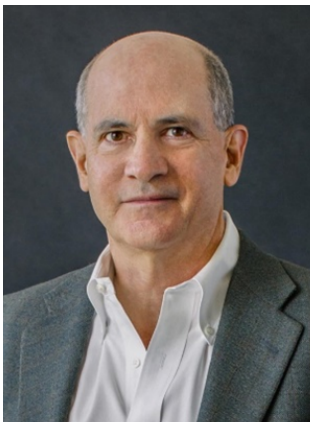
INTRODUCING OUR SPEAKERS

Usha Nekanti, PhD - UCI, Anderson Lab

Usha Nekanti is a postdoctoral fellow in Dr. Aileen Anderson's lab at UCI. She earned her master's degree in biotechnology from the University of Mysore, India. She completed her Ph.D. in Biomedical Science at UC Irvine in 2022 under Dr. Anderson's mentorship. Her research focuses on developing therapeutic strategies to regenerate the injured spinal cord by integrating biomaterials, neural stem cell transplantation, and modulating the injury environment with anti-inflammatory and regenerative factors.

Albert La Spada, MD, PhD - UC Irvine

In 2020, Dr. La Spada joined the faculty of the University of California Irvine as Distinguished Professor of Pathology & Laboratory Medicine and Neurology, and he founded the UCI Center for Neurotherapeutics which he directs. He currently serves as the Associate Dean for Research Development at the UC Irvine School of Medicine, and in 2023, Dr. La Spada was appointed as the Jack W. Peltason Endowed Chair by the Chancellor of the University of California Irvine in recognition of his academic accomplishments and commitment to collaborative research. Dr. La Spada's research is focused upon neurodegenerative disease, and he is seeking the molecular genetic events that underlie neuron dysfunction in SBMA, Huntington's Disease, spinocerebellar ataxia type 7 (SCA7), SCA2, ALS, Parkinson's disease, and Alzheimer's disease. He and his team have uncovered evidence for transcription dysregulation, perturbed bioenergetics, and altered protein quality control as contributing factors to cellular dysfunction in CNS diseases. By reproducing molecular pathology in mice and in neurons and other cell types derived from human patient stem cells, Dr. La Spada has begun to develop therapies to treat these disorders.



Thomas Rando, MD, PhD - UC Los Angeles

Thomas A. Rando, MD, PhD is Director of the Eli and Edythe Broad Center of Regenerative Medicine and Stem Cell Research at UCLA, where he is also Professor of Neurology and of Molecular, Cell, and Developmental Biology. Dr. Rando received his AB, MD, and PhD degrees from Harvard University and then completed a residency in neurology at UCSF and postdoctoral training at Stanford University. Prior to coming to UCLA in 2021, he had been on the faculty Stanford University School of Medicine in the Department of Neurology and Neurological Sciences. At Stanford, Dr. Rando was the founding Director of the Glenn Center for the Biology of Aging, a member of the Institute for Stem Cell Biology and Regenerative Medicine, founding deputy director of the Stanford Center on Longevity, and Chief of Neurology at the Palo Alto VA Medical Center.

Menú

Please be mindful of those who are dietary restrictions & allergies. Thank you!

All food will be served in the boardroom, directly behind the Conference Center.

BREAKFAST

Coffee, Tea, & Water (Iced & Hot)
Mini Muffins, Served with Butter & Jam - V
Mini Danish - V
Mini Scones - V

Additional Coffee, Tea, & Water will be available throughout the morning

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BUFFET LUNCH - YUCATAN BOWL

Mexican Rice - VG
Portobello Mushrooms - VG
Shredded Chicken
Braised Beef
Pico De Gallo - VG
Salsa Verde - VG

Romaine Lettuce - VG
Avocado Ranch Dressing - V
Charro Beans - V
Guacamole - VG
Dulce de Leche Brownie - V

Iced Tea
Water

All baked goods are made in a facility the uses nuts | Items will be labeled
V - Vegetarian | VG - Vegan | GF - *Gluten Friendly* | DF - Dairy Free

Menú

Please be mindful of those who are dietary restrictions & allergies. Thank you!

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AFTERNOON BREAK

Assorted Mini Cookies

ROAMING DINNER - MEDITERRANEAN INSPIRED

Greek Salad - V & GF

- Romaine, Kalamata Olives, Red Onion, Cucumber, Feta Cheese, Red Wine Vinaigrette

Harissa Shrimp Skewer - DF & GF

Chicken Souvlaki Skewer - GF

Mezzo Platter – VG & GF

- Hummus (V & GF), Tzatziki, (VG & GF) Marinated Olives, Roasted Pepper, Fennel and Zucchini, with Grilled Pita on the side (V)

Falafel - VG

Vegetable Samosa - VG

Vegetable Dolmas - VG & GF

Iced Tea, Lemonade, & Cucumber-Infused Iced Water

BAR

Ballast Point IPA

Corona Premier

Stella Artois (non-alcoholic)

Chardonnay

Point Noir

Champagne

Allagash White Ale

All baked goods are made in a facility the uses nuts | Items will be labeled

V - Vegetarian | VG - Vegan | GF - *Gluten Friendly* | DF - Dairy Free

Poster Presenters

1. **Tim McMullen** - *"Assessment and Enhancement of Natural Killer Cell-Mediated Anti-Tumor Immunity in Brain Metastasi"*
2. **Angel Ayala** - *"Ex vivo Graft Conditioning Reduces Graft-versus-Host Disease Following a Murine Allogeneic Transplant"*
3. **Abiageal R. Keegan** - *"Optimizing Gene Therapy for Duchenne Muscular Dystrophy Using Human iPSC-Cardiomyocytes"*
4. **Hung Doan** - *"TRF2 Alters Cardiomyocyte Cell Morphology of Healthy Cells"*
5. **Zahara Keulen** - *"Using Chemogenetic Manipulation to Study Second Messenger-Mediated Activation States in Microglia"*
6. **Alina Chadarevian** - *"Therapeutic Potential Of Human Microglial Transplantation For The Treatment of Sanfilippo Syndrome (MPS-IIIA)"*
7. **Tzu Chia Liu** - **"***Human Neural Stem and Progenitor Cell Secreted Factors Stimulate Vessel Lumen Formation"*
8. **Nicolette McClure** - *"Huntingtin Protein Interactors: Cell-Type Specific Interactors and RNA Binding Proteins"*
9. **Rostislav Brichko** - *"Adult D. Melanogaster Show Age-Dependent Decline in Dendrite Regeneration"*
10. **Fiona Lau** - *"Comparison of Muscle Promoters for Gene Therapy"*
11. **Marie Strauss** - *"How Do DNMT3A and NSD1 Mutations Alter DNA Methylation and Gene Expression to Drive Overgrowth Syndrome?"*
12. **Bin Lin, Ph.D.**- *"Vision Improvement in The Visual Cortex of a Severe Retinal Degenerate (RD) Rat Model After Retinal Progenitor Sheet Transplantation"*
13. **Vi Dang** - *"Sorting to Enrich for chemotherapeutic-resistant glioma Cells Based on Unique Membrane Properties"*
14. **Tracy Nhi Nguyen** - *"Alleviating Breast cancer Chemobrain Using Human Neural Stem Cell-Derived Extracellular Vesicles"*
15. **Elaine Lai** - *"Dual Vector Design for Duchenne Muscular Dystrophy Cardiomyopathy"*
16. **Jean Paul Chadarevian, Ph.D.** - *"Harnessing Human iPSC-Microglia for CNS-Wide Delivery of Amyloid-Targeting Proteins"*
17. **Dina El Tahlawy** - *"Repurposing Bezafibrate to Enhance Neural Stem Cell Engraftment and Locomotor Recovery in Spinal Cord Injury"*
18. **Devyani Swami** - *"Evaluating the Efficacy of miRNA Let-7 Derived From Human Neural Stem Cell Exosomes Against Radiation-Induced Cognitive Decline"*
19. **Casey Hudson** - *"Human Neural Stem Cell-Derived Extracellular Vesicles Protect The Brain Following Cranial Irradiation and Chemotherapy for Glioblastoma"*
20. **Sarah Soobin Lee** - *"A Synergistic Effect of Neural Stem Cell Co-culture With DRAK2 Inhibition to Induce Regulatory T cell Expansion"*
21. **Rosalyn Pham** - *"Identifying Extracellular Vesicles as a Potential Mechanism of Repair in Neural Stem Cell Lines"*

Poster Presenters

21. **Rosalyn Pham** - *"Identifying Extracellular Vesicles as a Potential Mechanism of Repair in Neural Stem Cell Lines"*
22. **Naomi Lomeli, Ph.D.** - *"Development of Translational Models of Ovarian Cancer-Associated Cognitive Impairments and Chemotherapy-Induced Peripheral Neuropathy"*
23. **Zachary Pope** - *"Cracking the Code of DNMT3A's Functions Beyond DNA Methylation"*
24. **Serena Phelps** - *"Spatial Characterization of Mitochondrial Function and Inflammation in Stem Cell Therapies for Spinal Cord Injury"*
25. **Alyssa Villegas** - "*Effect of C1q-CD44 Interactions on Microglial Phagocytosis"*
26. **Sebastien Colobong** - "*Notch Signaling Drug Induced MEGF10 Overexpression on Skeletal Muscle Stem Cells"*
27. **Nolan Huck** - "*Modeling Spinocerebellar Ataxia Type 7 Cone-Rod Dystrophy in Human Retinal Organoids"*
28. **Zeina Elrachid** - *"Intracellular C1q as a Potential Mediator of Microglial and Neural Stem Cell Behavior"*
29**. Laura Tennis** - "*Examining the Regulatory Role of N-glycan Branching in NSPC Differentiation"*
30. **Samir Malhotra** - "*Optimizing Retinal Organoid Generation: Comparative Protocols and Long-Term Culture in a Microfluidic Bioreactor System"*
31. **Pallabi Pal** - "*Effects of Antisense Oligonucleotides On In Vitro And In Vivo Mouse Model of VCP Multisystem Proteinopathy"*
32. **Emil Lundqvist** - "*Coupling of Topographical and Electrical Cues via Optoelectronic Material Interfaces to Drive Cardiomyocyte Maturation"*
33. **Sujeung Lim** - "*Complementary Peptide Coassemblies for Driving the Structural Order of Thermochromic and Phototransducer Nanomaterials"*
34. **Sydney Prange** - "*Dendrite Injury, but Not Axon Injury, Induces Neuroprotection in Drosophila Models of Neurodegenerative Disease*"
35. **Austin Silva & Sabrina Calderon - "***Uncovering the Impact of Uhrf1 Loss in Pancreatic Cancer"*
36. **Amanda Tedesco** - "*Human Muscle Stem Cell Senescence in Aging and Degenerating Rotator Cuff Tears"*
37. **Lan Weiss** - "*Development of Dual-Function AAV Vectors for Gene Therapy in Rare Genetic Muscle Diseases"*
38. **Alyaa Shmara** - *"Translational Studies in HSPB8- Associated Myopathy: Upregulating Autophagy With Trehalose in The iPSC-Derived Skeletal Muscle Progenitor Cells and Hspb8 Mouse Model."*
39. **Ruben Gonzalez** - *"Modeling Fragile X Syndrome Using Multi-Region Human Brain Organoids"*
40. **Javier Lepe** - *"Targeting of Mitochondrial Protein Magmas Enhances Sensitivity to GBM Treatment"*
41. **Dahlia Ordaz** - *"Investigating PARP Inhibitors as a Novel Approach to Chemotherapy Induced Cognitive Impairments in Ovarian Cancer Models"*
42. **Rongruo Zhang** - "Spinal and Bulbar Muscular Atrophy Cardiomyocytes Exhibit Arrhythmia"

Poster Presenters - Abstracts

Tim McMullen - #1

Uncontrolled proliferation of metastatic solid tumors accounts for most cancer-related deaths. Metastatic tumors in the brain exemplify several key difficulties associated with researching and treating metastatic disease, including poor tissue penetration by anti-neoplastic drugs and tight control of infiltrating immune cell function. Potentiation of brain-infiltrating effector immune cells represents a favorable strategy for the clinical management of brain metastasis. Natural killer (NK) cells have shown particular promise in this regard. Accumulating clinical and pre-clinical evidence supports a vital role for NK cells in anti-metastatic immunity and has prompted the rapid development of both NK cell engagers and adoptive NK cell transplants—both of which have entered clinical trials. Our work seeks to define NK cell anti-metastatic function in the brain with the goal of enhancing NK cell-mediated tumor control. We observe that NK cells rapidly infiltrate metastatic brain lesions but fail to control metastatic outgrowth. scRNA-seq has revealed functional deficits in brain-infiltrating NK cells relative to those infiltrating other organs. Our ongoing work seeks to characterize these deficits using functional assays and multiplex spatial immunophenotyping. We will demonstrate that NK cell functional deficiencies may be therapeutically targeted to improve metastatic control in the brain—with the end goal of rapid clinical translation in the adoptive NK cell therapy space.

Angel Ayala - #2

Hematopoietic cell transplantation (HCT) is a potentially curative therapy for a variety of blood disorders, but primarily relegated to patients with blood cancer due to post-transplant complications. Hematopoietic stem cells are the key component responsible for a successful HCT, due to their ability to self-renew, home the bone marrow niche, and re-establish the immune system following patient conditioning (i.e. chemo/radiotherapy). Non-self, allogeneic (allo)-HCT has the added benefit of graft-versus-tumor, and is largely carried out by cytotoxic T cells. Furthermore, allogeneic T cells are also responsible for generating a life-threatening complication called graft-versus-host disease (GVHD) wherein donor T cells become activated and mount an immune response against patient tissues. Most commonly, GVHD is treated by administration of immunosuppressive glucocorticoids to dampen the immune response of activated T cells. Despite the optimized regimen, many patients succumb to GVHD, highlighting a need for novel strategies to make HCT safer. Previously, we demonstrated that graft conditioning with glucocorticoids reduces GVHD severity and increases overall survival in a murine allogeneic transplant model. We sought to improve on this protocol by combining glucocorticoids, Bcl-2 inhibitors, and cytokines. Here we demonstrate that preconditioning graft cells with our cocktail reduces the culture time required, while maintaining low GVHD severity and high overall survival post-transplant. Our results implicate an important role for regulatory T cells in maintaining allogeneic tolerance and highlight a potential strategy to make allo-HCT a safer therapeutic.

Poster Presenters - Abstracts

Abiageal R. Keegan - #3

Duchenne Muscular Dystrophy (DMD) is a progressive, muscle-wasting genetic disorder that affects nearly 1 in every 5,000 live male births and ultimately leads to heart failure. DMD is caused by the lack of dystrophin expression; dystrophin stabilizes the sarcolemma of muscle cells by transducing force from the cytoskeleton to the extracellular matrix. The disease is particularly difficult to target via current gene therapy methods as the dystrophin transcript spans 14 kb, far exceeding the 5 kb packaging limit of AAV. A major challenge in the field is that dystrophic animal models do not recapitulate the cardiomyopathy observed in patients. To circumvent this challenge, I am using cardiomyocytes (CMs) differentiated from human induced pluripotent stem cells (iPSCs) to model the disease. DMD iPSC-CMs exhibit functional and morphological deficits. This platform enables investigation of the therapeutic efficacy of various gene therapy strategies. Synthetic variants of dystrophin, called microdystrophins, are currently being tested via clinical trial. Microdystrophins contain key domains of dystrophin and have been successful in rescuing disease characteristics of the skeletal muscle. But it is unknown if microdystrophin is effective in the DMD heart as these clinical trials are ongoing. DMD patients have no dystrophin expression at the tissue level and lose ambulation in their teens, ultimately succumbing to the disease in their mid-twenties. However, Becker muscular dystrophy (BMD) is a milder form of the disease, in which patients express a truncated dystrophin often at lower levels. Of particular interest is a BMD patient who retained the ability to walk at 61 years old, highlighting the functional nature of his dystrophin variant in the heart and skeletal muscle. This patient's dystrophin variant, called minidystrophin, is comprised of 50% of the full-length gene. We compare minidystrophin as a gene therapy in comparison to microdystrophins in clinical trials in DMD iPSC-CMs. We show that minidystrophin better rescues DMD phenotypes, including improved calcium handling and viability. These findings suggest that delivering larger dystrophin protein variants may be a better strategy to improve DMD patient outcomes.

Hung Doan - #4

TRF2 (Telomeric Repeat-binding Factor 2) is a homodimer and component of the Shelterin complex at the telomere. Telomeres prevent recognition of the free double-stranded breaks at the terminal ends of chromosomes, preserving DNA integrity and maintaining genomic stability. Our previous work with diseased cardiomyocytes differentiated from human induced pluripotent stem cells demonstrated that telomere attrition is a hallmark of disease. Overexpression of TRF2 to rescue telomere attrition also improved morphological deficiencies of diseased cardiomyocytes, suggesting that TRF2 may have extra-telomeric roles. To gain insight into the effects on cell morphology, we overexpressed TRF2 in healthy cardiomyocytes differentiated from H1 embryonic stem cells via lentivirus. We hypothesized that an overexpression of TRF2 would alter the expression of genes controlling cell morphology. Our data in H1-derived cardiomyocytes reveal an increase in cell size, a decrease in nuclear size and a decrease in sarcomere density following overexpression of TRF2. These results indicate that TRF2 may indeed have extra-telomeric roles when overexpressed. Given how cells respond to their microenvironment to maintain homeostasis, this study provides mechanistic insight into how cells control their morphology.

Poster Presenters - Abstracts

Zahara Keulen - #5

Calcium signaling is integral to many microglial signaling pathways implicated in neurodegeneration and inflammation. Microglia isolated from Alzheimer's Disease (AD) subjects exhibit altered calcium signaling, and microglia surrounding amyloid plaques in transgenic AD models exhibit increased frequency but lower amplitude calcium transients. Cytosolic calcium in microglia also increases following administration of inflammatory stimuli, and in response to cellular damage cues. These inflammatory and degenerative pathways converge upon calcium signaling, but there is little research determining how calcium dynamics alter microglia inflammatory responses in the context of degeneration. DREADDs (designer receptors exclusively activated by designer drugs) can be used to increase cytosolic calcium upon administration of an otherwise inactive drug. I generated a human induced pluripotent stem cell (iPSC) line that stably expresses hM3Dq, an excitatory DREADD. I then differentiated these cells into iPSC-microglia (iMGs) and examined the impact of CNO treatment on the transcriptome and function of human microglia. As expected, CNO treatment induces significant increase of calcium in the cytosol. RNA sequencing of CNO-treated cells further revealed many significant changes in gene expression, including increased transcripts related to mitochondria function and the induction of several cytokines and chemokines that are elevated in AD patient brains. CNO treatment also leads to increased levels of the chemokine CCL2 (MCP-1) in a time-dependent manner. These changes suggest that increasing calcium signaling may alter metabolism, drive recruitment of immune cells, and enhance phagocytosis in microglia.

Alina Chadarevian - #6

Sanfilippo Syndrome (MPSIIIA) is a pediatric lysosomal storage disease that leads to progressive neurodegeneration and shortened life span. MPSIIIA results from loss of function mutations in SGSH, a lysosomal enzyme critical for the degradation and recycling of heparan sulfates(HS). Recent evidence suggests that microglia express the highest levels of SGSH within the brain. Therefore, correction of SGSH mutations within microglia, or the transplantation of healthy microglia, could potentially increase levels of this enzyme, slowing or even preventing further neurodegeneration

To explore the potential for human microglia transplantation, we generated a novel xenotolerant mouse model of MPSIIIa via CRISPR-deletion of SGSH. Following histochemical and biochemical validation, SGSH KO pups were transplanted with PBS or human iPSC-microglia progenitor cells. After 4 months, mice were sacrificed, peripheral blood and liver collected and hemibrains collected for immunohistochemical and biochemical analysis and single nuclei RNA sequencing.

Initial analysis of 4-month old SGSH-KO mice reveals a dramatic increase in lysosomal content, gliosis, lipid accumulation, and elevated levels of nonreducing end heparan sulfates(HS-NRE). Remarkably, transplantation of human microglial progenitors significantly lowers lysosomal accumulation and reduces lysosomal content within murine neurons adjacent to engrafted human microglia. Biochemical analysis further revealed that microglia transplantation significantly reduces disease-specific HS-NRE. Ongoing experiments will further examine mRNA and protein levels to elucidate the impact of human microglial transplantation on other cell populations within the brain.

Together, these results provide the first evidence that iPSC-microglia could potentially be developed as a novel therapy for MPSIIIA and likely other lysosomal storage diseases.

Poster Presenters - Abstracts

Tzu Chia Liu - #7

Human neural stem and progenitor cells (hNSPCs) and human endothelial cells (hECs) are highly intertwined in early development, where the central nervous system is vascularized and perfused through vasculogenesis (de novo vessels formed from ECs), angiogenesis (growth of new blood vessels from pre-existing vasculature), and lumen formation (cord hollowing) [1,2]. In adulthood, hNSPCs may encourage vessel repair after neurovascular insults such as stroke or traumatic brain injury [3,4]. Our lab's bulk RNA and single-cell RNA sequencing (scRNAseq) data show hNSPCs express crucial vasculogenic, angiogenic, and lumen promoting factors [5,6,7]. Further, hNSPC conditioned media (CM) induces hEC vasculogenesis in 3D neurovascular scaffolds in vitro. Extracellular vesicles (EVs)/exosomes enriched from hNSPC CM have the same effect, and blocking exosome formation with inhibitor GW4869 disrupts hNSPC CM-induced vasculogenesis. Thus, hNSPC-secreted factors, particularly EVs/exosomes, promote vasculogenesis [8]. However, whether hNSPC secreted factors also induce lumen formation to permit blood flow is unknown. Here, we investigated the effects of hNPSCs on hEC lumen formation in a 3D neurovascular scaffold. We compared lumen formation across four conditions: hECs alone or with either hNSPCs, hNSPC CM, or CM from hNSPCs treated with an exosome inhibitor. HECs co-cultured with hNSPCs generated more vessels with lumens than hECs alone. HECs co-cultured with hNSPC CM showed enhanced lumen formation at similar levels as observed in hNSPC co-culture. However, blocking production of hNSPC exosomes with GW4869 exosome inhibitor decreased the effect of hNSPC CM. These results indicate that hNSPC secreted factors, specifically exosomes, are important for inducing lumen formation in 3D neurovascular scaffolds.

Nicolette McClure - #8

Huntington's disease (HD) is a devastating, genetic neurodegenerative disease that results in cognitive, psychiatric, and motor deficits. An abnormal CAG repeat expansion of ≥40 in the huntingtin gene (HTT), translated into a polyglutamine repeat expansion in the mutated protein (mHTT), is responsible for HD. There are currently no available disease-modifying treatments for HD and an effective treatment for HD depends on the comprehensive understanding of the causative disease protein functions and the disruption of those functions in the presence of the mutation. HTT is ubiquitously expressed in human cell-types, however, degeneration of the medium spiny neurons (MSNs) of the striatum and atrophy of the cortex are hallmarks of HD, while brain regions such as the cerebellum are relatively spared in disease. Growing evidence also suggests that transcriptional and morphological changes in the non-neuronal maintenance cells of the brain—astrocytes and microglia—contribute to progression of the disease. HD is associated with dysfunction of tissues outside of the brain including the heart and the gut. This cell-type specific mHTT-related dysfunction suggests a novel cell-type specificity to HTT function. Previous HTT interaction studies and our recent data have identified RNA-binding proteins (RBPs) as prominent HTT interacting partners. RBPs are critical in cell-fate determination due to their role in regulation of gene expression via alternative RNA splicing, a processing step in which one transcript may be spliced into multiple different mRNAs that encode different proteins. In addition, transcriptional dysregulation has been well described in HD and data from our lab supports the growing evidence of splicing deficits and emergence of cryptic exons in HD. This dysfunction along with HTT's extensive interaction with RBPs suggests a role for HTT in post-transcriptional regulation potentially as a scaffold for RBPs—a function that is disrupted with mHTT. This thesis proposal hypothesizes that: 1) HTT-interacting partners, and therefore HTT function, are cell-type specific leading to cell type specificity in disease and 2) HTT has a role in post-transcriptional regulation by functioning as a scaffold for RBPs. In Aim1, I am using transcriptomics and proteomics to identify the cell-type specificity of HTT interactors both within the brain and outside the brain comparing MSNs, cortical neurons, astrocytes, microglia, cardiomyocytes, and intestinal epithelial cells. To achieve this, I am using a novel isogenic induced pluripotent stem cell (iPSC) set of lines with a biotin ligase (TurboID) fused in-frame to HTT or mHTT to label protein and RNA interactors. In Aim 2, I will examine the role of HTT as a post-transcriptional splicing regulator in the most affected cell type: MSNs. I will investigate 2A) splicing regulated by two prominent RBPs, FUS and TDP43, within the context of HTT and mHTT, using FUS/TDP43 knockdown (KD) as a baseline for dysregulated splicing, and 2B) investigate the dependency of FUS/TDP-43 regulated splicing on HTT using HTT KD within the TurboID lines.

Poster Presenters - Abstracts

Rostislav Brichko - #9

Neuronal dendrites undergo age-related structural changes that may contribute to circuit and synaptic dysfunction before neurons die. While dendrites can regenerate after injury in aging animals, regeneration becomes increasingly limited with older age. Manipulating insulin metabolism by dietary restriction can increase lifespan in a variety of animal model systems and may boost dendrite regeneration. The cellular and molecular mechanisms by which insulin metabolism affects dendrite regeneration in aging adults are unknown. We hypothesize that extending an organism's lifespan may enhance the health span of neurons to boost dendrite regeneration after injury, especially in older animals and at later stages after injury. Here, we show that older adult Drosophila melanogaster continue to regenerate their dendrites for weeks after injury. While regeneration in older animals is more significant than previously appreciated, in wild-type animals it does not fully recover total dendrite length and area coverage. Our work also investigates whether intervening in insulin signaling may boost dendrite regeneration in older adult Drosophila. Together this demonstrates an increased ability of neurons to regenerate after injury in older animals, and a potential avenue to further boost regrowth after trauma.

Fiona Lau - #10

Gene replacement therapy can be an effective approach to treat neuromuscular diseases caused by the lack of gene expression. Adeno-associated virus (AAV) is an efficient vehicle used to deliver genes systemically to the skeletal muscles, diaphragm, and the heart. A major limitation to AAV-mediated gene therapy is the packaging limit of 4.7 kb, which must include the inverted terminal repeats (viral elements), promoter, and gene of interest. While the inverted terminal repeats are of a fixed size, the promoter can be optimized to be tissue-specific and small, making room for larger genes. For neuromuscular diseases like Duchenne muscular dystrophy (DMD), in which the gene of interest is over 11 kb, identifying the smallest promoter that can enable gene expression is critical for design. Our goal was to test various muscle promoters in inducing the expression of genes in human cells. We cloned the muscle creatine kinase promoter and variations of this promoter into a vector driving the expression of luciferase. We compared the strength of these promoters against a ubiquitously expressed promoter (EF1a) and a cardiac promoter (TNNT2) in myotubes and cardiomyocytes differentiated from human induced pluripotent stem cells (iPSCs). We discovered that the CK8 promoter may be the optimal promoter for AAV delivery methods due to its small size and robust expression in human myotubes and cardiomyocytes. The identification of this promoter provides new insight on the optimal design strategy for the treatment of neuromuscular diseases.

Poster Presenters - Abstracts

Marie Strauss - #11

Germline mutations in epigenetic modifiers DNMT3A and NSD1 cause similar phenotypes of overgrowth syndrome with intellectual disability (OGID). NSD1 is a histone methyltransferase that mono/dimethylates lysine 36 of histone 3 (H3K36me1/2). DNMT3A is a de novo DNA methyltransferase that reads H3K36me2 in addition to other histone marks. The molecular mechanism of how these two methyltransferases interact as well as how they lead to OGID is not yet understood. We hypothesize that mutations in these two genes impact the same molecular pathway to cause their common overgrowth phenotype. To test this hypothesis, we use human embryonic stem cells to model OGID-associated mutations of DNMT3A and NSD1. By inducing these mutations in the same cell line, we minimize background epigenetic noise and let the epigenetic variations caused by these mutations come to the foreground. We collected DNA methylation data of over 850,000 genome-wide loci and RNA-Seq data. We are currently integrating analyses to discover common underlying mechanisms in these disorders with similar phenotypes.

Bin Lin, Ph.D. - #12

On day 19 of gestation (day of conception day 0), fetuses were removed by cesarean section from timed-pregnant rats. Dissected retinas were incubated in BDNF/GDNF microspheres overnight at 4°C, and then transplanted to the subretinal space of Rho S334ter-3 retinal degeneration (RD) rats. Development of transplants was monitored by high resolution optical coherence tomography (SD-OCT). The visual function was assessed by optokinetic test (OKT) and single-unit cortical recording using multi-electrode arrays, from higher visual areas (anterior lateral [AL] and lateral medial [LM] cortex). Sinusoidal gratings with optimized parameters and natural images were used to measure details of the receptive fields. Cryostat sections through transplants were stained with hematoxylin & eosin (H&E); or processed for immunohistochemistry (IHC) to label donor cells, retinal cell types and synaptic markers.

Retinal degenerate diseases lead to profound vision loss in millions of people worldwide. Hence, there is a great demand for the development of efficient techniques that allow for long-term vision restoration. In this study, we transplanted dissected retinal progenitor sheets, which can differentiate into photoreceptors and integrate with the host retina of rats with severe retinal degeneration. Remarkably, we not only show vision improvement by optokinetic test, but also show visual responses in cortex similar in quality to normal rats. This study proves the concept that the retinal progenitor sheets can provide a clinically applicable strategy to cure blindness.

Poster Presenters - Abstracts

Vi Dang - #13

Glioblastoma, astrocytoma, and oligodendroglioma comprise a class of aggressive and deadly brain tumors called diffuse gliomas. Around 20,000 glioma cases are diagnosed yearly in the US alone. The current standard chemotherapy treatment, temozolomide (TMZ), is insufficient as the 5-year survival rate of glioblastoma patients is as low as 8%. This is due to the presence of TMZ-resistant cells within tumors that lead to chemoresistance and tumor recurrence. Thus, studying the molecular properties of TMZ-resistant cells would enable more effective means of targeting them and thus improve patient outcomes. We leveraged dielectrophoresis (DEP), a phenomenon by which non-uniform electric fields induce differential movement of cells, as a novel label-free technique to sort glioma cells based on their membrane electrophysiological properties. We were able to successfully use DEP to sort cells from glioblastoma and oligodendroglioma established cell lines, which yielded fractions that differed in membrane capacitance, the membrane's ability to store charge. Interestingly, the DEP-sorted cell fractions also exhibited significant differences in TMZ resistance, indicating that we were able to use DEP to enrich for TMZ-resistant cells. Further, the differences in TMZ resistance were coupled with their membrane capacitance differences. Because we previously found that changes in membrane capacitance were linked to differences in glycosylation, we utilized lectin analysis to assess glycan expression of DEP-sorted oligodendroglioma cells. Our data show that TMZ-resistant oligodendroglioma cells enriched from DEP sorting had reduced levels of mannose glycans compared to less TMZ-resistant fractions. Collectively, our novel findings demonstrate (a) TMZ-resistant glioma cells can be enriched by DEP, and (b) TMZ resistance is correlated with membrane capacitance and cell surface glycosylation. These findings could enable further characterization of TMZ-resistant cells to better understand molecular mechanisms of TMZ resistance and the development of more effective treatment strategies for gliomas through targeting membrane properties such as glycosylation.

Tracy Nhi Nguyen - #14

Breast cancer is one of the most common cancers affecting women and the second most frequent cause of Central Nervous System (CNS) metastases. Cytotoxic chemotherapies to thwart tumorigenesis have been shown to cause cancer-related cognitive impairments (CRCI), negatively affecting the quality of life (QOL) for 65-75% of survivors. Currently, there are approximately four million women with a history of breast cancer in the U.S. Often referred to as chemobrain, CRCI encompasses decreased attention span, slower processing speeds, disrupted executive function, and issues with memory consolidation and recall during or after treatment. Previously, we have demonstrated the regenerative potential of extracellular vesicles (EVs) derived from human neural stem cells (hNSCs) in reversing CRCI in irradiated brain cancer mouse models. The current study focuses on a breast cancer mouse model to assess the effectiveness of EV treatment derived from a GMP-ready hNSC line (UCI-191) for chemobrain. EVs are lipid-bound nano-sized vesicles that cross the blood-brain barrier and contain bioactive cargo such as lipids, proteins, nucleic acids, and mitochondrial components. The study utilizes a syngeneic, WT C57BL/6J mouse breast cancer model. Murine Py230 cancer cells, with an epithelial-like morphology, form adenocarcinoma tumors in the mammary fat pads. Mice received a clinically relevant adjuvant chemotherapy regimen, including Adriamycin (ADR, doxorubicin, 2mg/kg) and cyclophosphamide (CYP, 50mg/kg), administered an hour apart, once weekly for four weeks. This regiment eliminated cancer growth. After the administration of chemotherapy, mice received hNSC-EV treatment intending to ameliorate the CRCI. Mice received IV (retro-orbital vein, RO) injections (once weekly for four weeks) and were administered learning and memory, executive function, and memory consolidation cognitive function tests. Animal brains were further evaluated for neuroinflammation, gliosis, and synaptic integrity. We found that mice treated with ADR-CYP showed significantly reduced learning and memory, increased anxiety, decreased memory consolidation, and impaired executive function compared to ADR-CYP-treated mice receiving EVs. Immunofluorescence analyses revealed significant improvements in synaptic integrity and reductions in astroglial and microglial activation in the EV-treated mice. These findings demonstrate the regenerative and neuroprotective impact of stem cell-derived EVs in ameliorating breast cancer chemobrain that has the potential to improve QOL for millions of breast cancer survivors.

Poster Presenters - Abstracts

Elaine Lai - #15

Duchenne muscular dystrophy (DMD) is an X-linked muscle wasting disease that affects every 1 in 5,000 males. Onset of symptoms starts around two years of age and includes loss of ambulation, respiratory problems, and cardiac complications with heart failure being the leading cause of death for DMD patients in their late 20s. Dystrophin is a 427 kDa protein encoded by an 11 kb transcript. Dystrophin connects the actin cytoskeleton of muscle cells to the extracellular matrix and protects cells from contraction-induced injury. DMD is caused by various mutations in the dystrophin gene that either result in the lack of dystrophin or expression of a truncated dystrophin. There are ongoing gene therapy clinical trials to test the efficacy of smaller variants of dystrophin called microdystrophins. These dystrophin variants are only one third the size of full-length dystrophin due to the 4.7 kb packaging limit of adeno-associated virus (AAV). Previous studies show that microdystrophins improve skeletal muscle function in mdx mice but the effects on the heart are unknown as these mice do not recapitulate the severe cardiomyopathy as seen in DMD patients. In one case study, a patient with Becker muscular dystrophy, a milder form of dystrophinopathy, expressed a dystrophin variant missing 46% of the protein. Despite expressing this truncated dystrophin variant at low levels, this Becker patient was still ambulatory at 60 years of age and passed away in his 70s. Therefore, our lab hypothesizes that this dystrophin variant harboring the Becker mutation, ΔH2-R19, can improve the cardiac deficits of DMD. In this study, I use cardiomyocytes differentiated from human induced pluripotent stem cells (iPSC-CMs) to study the disease in the molecular context of human cells. We observe hallmarks of disease, including poor calcium handling and lower force of contraction, in DMD iPSC-CMs. Since ΔH2-R19 exceeds the packaging capacity of AAV, I use a two vector AAV system engineered with a split intein that can undergo protein trans-splicing in cells to deliver this dystrophin variant to DMD iPSC-CMs. This dual vector strategy enables delivery of a dystrophin variant twice the size of the ones currently being administered to patients and holds therapeutic potential in delaying the onset of heart failure.

Jean Paul Chadarevian, Ph.D. - #16

Studies have sought to circumvent the protective qualities of the blood-brain barrier to deliver therapeutic proteins for the treatment of neurodegenerative diseases. Yet, brain-specific uptake, peripheral toxicity, off-target effects, and repeated dosing present considerable challenges. In this study, we sought to determine whether human iPSC-microglia (iMG) could be genetically engineered ex vivo to enable pathology-responsive delivery of therapeutic proteins to the brain.

We first examined the transcriptional responses of human iMG in chimeric models of breast cancer brain metastasis, multiple sclerosis-associated demyelination, and Alzheimer's Disease (AD), demonstrating microglia adopt diverse transcriptional responses as they encounter differing brain pathologies. Using a novel xenotolerant model of AD lacking the Csf1r-FIRE enhancer (5x-hFIRE) we further found a strong correlation between microglial CD9 expression and beta-amyloid deposition throughout the brain. As proof of principle, we then CRISPR-edited human iPSCs to express the beta-amyloid degrading enzyme neprilysin (NEP) or secreted neprilysin (sNEP) downstream of the endogenous CD9 promoter. iPSC-microglial progenitors were then differentiated and transplanted into 2-month-old WT-MITRG and 5x-MITRG mice for 4.5 months before brains were harvested for immunohistochemistry and biochemical analysis.

Poster Presenters - Abstracts

Dina El Tahlawy - #17

Spinal cord injury (SCI) results in mitochondrial dysfunction due to oxidative stress, nutrient deprivation, and pro-inflammatory conditions. Human neural stem cells (hNSC) represent a promising therapeutic strategy for addressing traumatic injuries. Previously, transcriptomic analysis of multiple UCI-hNSC revealed critical distinctions in five bioenergetics, 2) biogenesis, 3) permeability transition, 4) redox potential and 5) mitophagy. Using a drug repurposing platform, FDA-approved therapeutics were identified to enhance hNSC efficacy. Functional mitochondrial assays such as the genetically encoded ATP sensors (iATPSnFR ATP Reporter, addgene #102551) and Seahorse XF Metabolic Analyzer were performed. The results demonstrated that the UCI152 cell line responded more favorably to biogenesis-enhancing therapeutics, leading to the identification of Bezafibrate as a candidate to enhance stem cell transplantation and engraftment in the SCI model.
To investigate if in-vitro pretreatment of hNCs with Bezafibrate will enhance their survival and engraftment in vivo, Rag1 mice were given a unilateral C5 cervical contusion injury and transplanted 4 weeks later with wild-type UCI lines (UCI161 and UCI152) or Bezfibrate pretreated hNSC. Locomotor recovery was assessed through the Basso Mouse Scale (BMS) and Cylinder behavioral tasks, indicating significant locomotor improvements in mice receiving the drug-pre-treated UCI152 cells. To identify this repair mechanism, we performed immunohistochemical analysis of the engraftment stems cells utilizing human-specific Stem121 antibody combined with lineage specific marker for the cell fates of hNSC: DCX (neurons), oligodendrocytes (Olig2) and astrocytes (Stem123). Using unbiased stereology, we showed that pre-treated UCI152 were able to engraft almost as efficacious as the UCI161 (positive controls) and differentiated to 45% oligodendrocytes. In conclusion, our results indicate that stem cell engraftment in the SCI model is closely associated with improved locomotor recovery as evidenced by behavior assessments and confirmed through stereological quantification of the transplanted cells.

Devyani Swami - #18

With the rising incidence of brain and nervous system tumors in individuals under the age of 20, therapeutic strategies for managing these cancers are continuously evolving. Cranial radiation therapy is the mainstay for brain tumors, yet it causes long-lasting cognitive impairments that negatively impact the quality of life of cancer survivors. In search of safer and more efficacious therapy, we have been working on human neural stem cells (hNSC) derived extracellular vesicles (EVs) to ameliorate radiation-induced cognitive impairment. One promising yet underexplored approach is the in vivo expression of miRNA via recombinant Adeno Associate Virus (rAAV)-mediated delivery, which may offer distinct advantages over other treatment strategies. Previously, our team showed that transplanting hNSCs into the hippocampus improves radiation-induced cognitive deficits in mice. hNSC-derived EVs contain miRNAs, which modulate NSC survival, expansion, differentiation, and neuroinflammation. Subsequently, we found that locally administered hNSC-derived EVs with miR-124 can alleviate radiation-induced cognitive impairments. In Parallel, RNA sequencing of the GMP-compliant hNSCs revealed multiple miRNA candidates, with let-7 being the most abundant. In our current work, we will investigate AAV-mediated miRNA let-7 expression in the WT mouse hippocampus following clinically-relevant fractionated irradiation and adjuvant temozolomide treatment. Furthermore, we will study the neuroprotective efficacy of miRNA let-7 using a battery of behavioral tests to mitigate radiation-induced cognitive impairments. This study marks a novel effort in evaluating the therapeutic efficacy of miRNA let-7 with and holds a significant promise in advancing translational strategies to reverse radiation-induced brain injury.

Poster Presenters - Abstracts

Casey Hudson - #19

CNS cancers are debilitating, with survival rates around <30%. Brain cancer survivors often grapple with cognitive dysfunction and neuroinflammation post-cranial irradiation (CRT) and chemotherapy (temozolomide, TMZ) treatments. As survivorship increases, therapeutic interventions for these side effects are becoming a priority. Our previous research showcased the neuroprotective and regenerative properties of human neural stem cell (hNSC)-derived extracellular vesicles (EVs) post-acute 9 Gy CRT. These nano-scale lipid-bound vesicles carry bioactive cargo and traverse the blood-brain barrier. In this study, immunocompetent C57/Bl6 mice were induced with brain cancer using a murine CT2A astrocytoma line followed by a clinically relevant CRT-TMZ treatment regime. Two days post-treatment, EVs isolated from two GMP-derived hNSC lines (Shef6, UCI-191) were administered intravenously through retro-orbital vein injection, and their impact on cognitive function, neuroinflammation, and synaptic integrity was determined 1-month later. EVs significantly enhanced cognitive function in CRT-TMZ-exposed astrocytoma-bearing mice. Immunofluorescence analyses revealed significant improvements in synaptic integrity and reduced gliosis, indicating the neuroprotective efficacy of GMP-derived EVs following brain cancer treatment.

Sarah Soobin Lee - #20

Multiple sclerosis (MS) is an autoimmune disease where autoreactive T cells attack the central nervous system. Current therapies make patients vulnerable to infection and cancer during treatment, emphasizing the need for safer approaches. Previous study shows that DAP kinase-related apoptosis-inducing protein kinase 2 (DRAK2)-deficient mice are resistant to experimental autoimmune encephalomyelitis (EAE) without any defect in T cell recruitment to CNS upon infection. Drak2-/- T cells show increased Treg numbers upon activation, and mouse in vivo data demonstrates that the increased number of Treg is responsible for EAE resistance in Drak2-/- mice. Besides, recent studies on neural stem cells (NSCs) in treating autoimmune diseases discovered that NSC injection into mice induces Treg differentiation and this leads to remyelination in mice with EAE. We found that NSC co-culture with mouse T cells from Drak2-/- show larger expansion of Tregs upon T cell activation, which can serve as good treatment in mice when used in in vivo experiment. Newly synthesized DRAK2 inhibitors showed promising results with a decrease in lipid content with increased Treg numbers upon treatment in vitro. Further studies by NSC injections in mice along with DRAK2 inhibitor treatment in vivo may show synergistical effect with notably higher EAE resistance, which can offer a new avenue on a future MS therapeutics development.

Poster Presenters - Abstracts

Rosalyn Pham - #21

Spinal cord injury (SCI) is a debilitating condition characterized by an ischemic secondary phase that induces mitochondria dysfunction and neuroinflammation. Previous transcriptome analysis of two human neural stem cell (hNSC) lines developed and characterized – UCI161 (efficacious) and UCI152 (non-efficacious) – revealed that they differed in five key mitochondria functions: 1) biogenesis, 2) bioenergetics, 3) mitophagy, 4) membrane permeability, and 5) redox potential. Using an FDA-approved drug repurposing platform, the biogenesis drug Bezafibrate was identified as a favorable candidate for modulating hNSC efficacy by enhancing their TFAM levels, mitochondrial mass, engraftment, and survival. In vivo, behavioral assessments, such as the Basso Mouse Scale (BMS) and cylinder, revealed that transplanting the Bezafibrate pretreated UCI152 line provided functional recovery despite its previously low engrafting profile.

Interestingly, our prior studies have suggested that hNSC fitness and therapeutic capacity might be reflected in the extracellular vesicles (EV) they secrete, which include non-coding RNA, proteins, and mitochondria. EV isolation, RNA isolation, and RNA sequencing were performed, revealing that the efficacious UCI161 exhibited higher expression of genes associated with oligodendrogenesis, remyelination, and synaptogenesis. Additionally, the EV cargos contain mitochondria DNA encoded genes, suggesting mitochondria transfer as well as a key non-coding RNA in the efficacious line that plays a role in neural development and mitochondria biogenesis. We hypothesize that the secretome of the efficacious line contains factors that would be pro-regenerative. Given the promising impact of Bezafibrate pretreatment, future studies can integrate drug-repurposing and EV transfer to better understand the mechanism that underlies this recovery. Our future project targets EV transfer as a potential mechanism of SCI repair by evaluating the secretomes of the pretreated lines for pro-regenerative elements that align with the observed functional enhancement.

Naomi Lomeli, Ph.D.- #22

Cancer-related cognitive impairments (CRCI) and chemotherapy-induced peripheral neuropathy (CIPN) are debilitating consequences of platinum-based chemotherapy (e.g., cisplatin). More than 30% of non-central nervous system cancer patients report experiencing cognitive impairments prior to chemotherapy treatment, which suggests that cancer may contribute to neurological impairments independently of chemotherapy. Cisplatin is widely used to treat ovarian malignancies, and over 70% of women experience CRCI during and after platinum-based chemotherapy. Most studies of CRCI have been conducted in healthy non-cancer bearing rodents, which are not phenotypically representative of cancer patients. To examine the contribution of cancer itself and additional neurological impairment with chemotherapy, we used the ID8 syngeneic ovarian cancer mouse model and assessed cognition and hyperalgesia +/- cisplatin treatment. METHODS: B6 female mice were injected with 107 ID8 cells or 0.9% saline, i.p. Mice received cisplatin (2.3 mg/kg/day, i.p.) or 0.9% saline (OvT+CIS, OvT+VEH, respectively) for 5d, followed by 5d of rest for two cycles. Anxiety-related behavior and cognition was assessed longitudinally using the open field test (OFT), novel object recognition (NOR) and novel place recognition (NPR). Cold and mechanical hyperalgesia was also assessed longitudinally. RESULTS: Ovarian tumor-bearing mice treated with or without cisplatin showed a significant increase in anxiogenic behavior in the OFT, and impairments in NOR and NPR, 4 weeks post-cisplatin completion, compared to non-tumor bearing control mice. ID8 cancer bearing mice developed a significant increase in sensitivity to mechanical and thermal (cold) stimuli as early as 2 weeks post-tumor implantation, compared to non-tumor controls. Cisplatin transiently increased hyperalgesia in OvT+CIS mice, which persisted longitudinally in OvT+VEH mice. Serum cytokine levels were elevated in OvT+VEH mice (IL-2, IL-10, INFγ) and OvT+VEH rats (IL-4, IL-10) compared to OvT+CIS ($P<0.05$). DISCUSSION: This is the first rodent model to demonstrate that ovarian cancer may induce neurocognitive and sensory changes in the absence of chemotherapy, which supports the observations of memory impairments and chronic pain experienced by people with ovarian cancer. Future studies will address hyperalgesia and cognitive differences between healthy control and ovarian cancer models +/- cisplatin, and biological mechanisms underlying CRCI and CIPN.

Poster Presenters - Abstracts

Zachary Pope - #23

DNMT3A, a key enzyme responsible for de novo DNA methylation, plays a critical role in gene regulation. Mutations in DNMT3A are commonly associated with Clonal Hematopoiesis of Indeterminate Potential (CHIP) and Acute Myeloid Leukemia (AML) and are linked to an increased risk of cardiovascular disease and blood cancers. While DNMT3A's methyltransferase function is relatively well studied, a recent report and our unpublished data suggest that DNMT3A has a catalytic activity-independent role in gene regulation, such as RNA splicing and enhancer activation. These newly discovered roles of DNMT3A may underlie some of the disease phenotypes associated with DNMT3A mutations, but traditional gene knockout models do not allow decoupling DNMT3A's enzymatic activity from its other functions. To investigate DNMT3A's broader functions, we are developing a human embryonic stem cell (hESC) model with dTAG-mediated, inducible and rapid degradation of DNMT3A, enabling precise temporal control over its depletion. This system, combined with the use of catalytic-dead mutant, will enable us to explore DNMT3A's role in gene regulation independent from its DNA methyltransferase activity. This model will allow us to further understand DNMT3A's regulatory functions, aiding in uncovering mechanisms underlying CHIP and AML and potentially identifying new therapeutic targets.

Serena Phelps = #24

Spinal cord injury (SCI) is a debilitating neurological and physiological condition that damages the central nervous system (CNS), causing the death of neurons and oligodendrocytes, resulting in loss of sensory and/or motor function. Human neural stem cells (hNSCs) have shown great promise in pre-clinical and clinical therapies for treating traumatic injuries. Previously, transcriptomic analysis of two hNSC lines derived in our lab, UCI161 (efficacious) and UCI152 (non-efficacious), revealed differences in key mitochondria functions termed as mitochondria fitness traits (MFTs): bioenergetics (fusion and fission balance), redox signaling and mitochondria permeability transition, mitophagy, and biogenesis. Using a drug repurposing platform, FDA-approved or clinically-relevant pharmacological agents were identified to modulate MFTs and enhance hNSC efficacy. Drug screening in-vitro identified a biogenesis drug candidate (Bezafibrate) that enhanced TFAM levels, mitochondrial mass, and cell proliferation. In the current study, we aim to develop a method using Hyperion spatial profiling to assess whether Bezafibrate pre-treatment is able to improve the "efficacy" of hNSCs in-vivo. Using immunohistochemistry, we characterized the concentration/localization of ~30 antibodies in categories of inflammation and mitochondria fitness. We examined inflammation levels using markers such as NLRP3, IL-1β, Caspase-1, and iNOS. Cell types were identified using human-specific marker STEM121, and immune cell types using markers such as Iba-1, CD68, MAC2, Ly6G, and F4/80. This allows for quantification of cell engraftment/differentiation and subpopulation density of immune cells. Their polarization state is detected by assessing the expression of pro-inflammatory M1 (iNOS, IL-6) and pro-regenerative M2 (Arginase-1, IL-10) players. We also examined the expression of MFT targets (such as NRF1, NRF2, SOD2, TFAM, OPA-1, etc.) in the STEM121+ hNSCs. In conclusion, establishing this novel multiplexed mapping system allows for assessment of processes including mitochondria transfer and retention of complex MFT profiles in-vivo, which has previously not been possible using traditional

Poster Presenters - Abstracts

Alyssa Villegas - #25

Spinal cord injuries (SCI) are extremely debilitating and impact thousands of lives. The first responders to SCI are microglia, the resident immune cell of the central nervous system responsible for phagocytosing debris. Microglial phagocytosis is vital for repairing the central nervous system following a SCI because it eliminates dead cells and debris from the injury epicenter. However, the mechanisms regulating microglial phagocytosis remain only partly understood. It is known that complement protein C1q is present at high levels in the injury epicenter and that it tags debris for phagocytosis by microglia. Moreover, our lab recently identified five novel C1q receptors, including CD44 which holds an established role as a phagocytic receptor. Taken together, I hypothesize that C1q binds to CD44 on the microglial membrane to mediate phagocytosis. To test this hypothesis, I treated wild-type and CD44 knockout(KO) induced pluripotent stem cell-derived microglia(iMGL) with C1q-tagged pHrodo, which will fluoresce red in response to the change in acidity that occurs once it enters the microglial cytoplasm. I then used flow cytometry to quantify the percentage of microglia that are phagocytosing C1q. Additionally, microscopy was used to visualize and validate that the particles are internal to the cell. I found that CD44 KO iMGL phagocytose at elevated levels when compared to WT iMGL, indicating that CD44 is a crucial regulator of microglial phagocytosis. Overall, characterization of C1q-CD44 interactions holds the potential to lead to a therapeutic that manipulates the relationship between the two to help people recover from a SCI.

Sebastien Colobong - #26

Satellite cells (SCs) are the main drivers of muscle regeneration. SCs reside in niches within the muscle, interacting with surrounding myofiber and basal lamina. The niche is critical to supporting SCs, and its disruption can cause SC pool depletion or senescence leading to muscular dystrophies. A therapeutic approach for these myopathies is to generate healthy skeletal muscle progenitor cells (SMPCs) derived from patient-specific iPSC cells and engraft them into patients to promote muscle regeneration. However, SMPCs are functionally immature, resulting in inefficient stem cell engraftment in vivo. Previous studies from our Lab used Spatial Transcriptomics to identify MEGF10 as an important receptor expressed by engrafted fetal SMPCs that repopulate niches. MEGF10 is involved in the Notch signaling pathway and it has been described to regulate developmental muscle stem cell niche formation but its exact mechanism in engrafted human SMPC niche formation remains unclear. This study proposes the usage of Notch signaling drugs to recapitulate a MEGF10 overexpression phenotype in vitro. However, one setback was our inability to replicate SC niche interactions with surrounding basal lamina and myofibers. To resolve this, we adapted a recently published decellularization approach from the Crosbie Lab to human muscle which yielded an acellularized extracellular matrix and seeded these with iPSC-myotubes. We found myotubes grown on these myoscaffolds enabled 20% more attachment after 15 days of differentiation. These myoscaffolds thus provided a platform to study MEGF10 overexpression via Notch signaling drugs. This study will define MEGF10's role in SC niche formation by observing changes in related phenotypes such as SC density, SC localization within the niche, myofiber coverage, and SC proliferation. Further understanding of MEGF10's function in niche formation will allow for improvement in SC engraftment therapies.

Poster Presenters - Abstracts

Nolan Huck - #27

Spinocerebellar ataxia type 7 (SCA7) is a neurodegenerative disease uniquely characterized by cone-rod dystrophy, leading to severe vision impairment and blindness. SCA7 results from CAG-polyglutamine (polyQ) repeat expansion in the Ataxin-7 (ATXN7) gene, disrupting transcriptional regulation and epigenetic remodeling in retinal photoreceptors. Current understanding of SCA7 retinal degeneration is limited, necessitating advanced models to uncover disease mechanisms. This study utilizes human induced pluripotent stem cell (iPSC)-derived retinal organoids (ROs) to model SCA7 cone-rod dystrophy. These 3D organoids recapitulate the structural and cellular organization of human retina, including rod and cone photoreceptors. SCA7 ROs derived from patient iPSCs demonstrate disease-relevant phenotypes, including transcriptional dysregulation and altered epigenetic landscapes. ROs will be characterized across developmental stages using optical coherence tomography, light microscopy, and immunohistochemistry to assess retinal layer formation, photoreceptor differentiation, and ultrastructural morphology. Transmission electron microscopy will provide detailed insights into photoreceptor outer segment integrity and synaptic organization. This work highlights the potential of iPSC-derived ROs to unravel the molecular basis of SCA7 retinal degeneration and to serve as a platform for therapeutic development.

Zeina Elrachid - #28

Spinal cord injury (SCI) is a destructive condition resulting from trauma in which the spinal cord undergoes damage such as bruising or tearing. This damage is associated with a disruption of the blood-spinal cord barrier and a subsequent influx of molecules and cells from the bloodstream into the injured microenvironment. One such protein infiltrating the injured niche in high concentrations is C1q. While the role of C1q as the initiator of the complement cascade is well-characterized, it remains unclear how C1q influences cells in the central nervous system (CNS). Prior studies in the lab have revealed that C1q drives activation of microglia, the immune cells of the CNS. While this initial microglial activation is essential for the injury response, microglia maintain an activated state for years following SCI, causing persistent inflammation, excessive glial scarring, and chronic pain. Additionally, our lab has shown that in the injured niche, C1q exposure alters the migration and fate of transplanted human neural stem cells (hNSC). Therefore, characterizing the mechanisms of C1q-driven changes in CNS cell behavior could inform therapeutic development to alleviate chronic inflammation and increase hNSC transplant efficacy. With this goal, I used purified human C1q to characterize its interactions with five novel receptors our lab recently identified: ADCY5, BAI1, CD44, cMET, and GPR62. Previous proximity ligation assay (PLA) data has validated cell-surface interactions between C1q and the candidate receptors in both induced pluripotent stem cell-derived microglia (iMGL) and hNSC. To test whether these C1q-receptor complexes become internalized, I treated iMGL with C1q and performed quantitative PLA following cell permeabilization. Most notably, the number of C1q-CD44 interactions following C1q exposure exhibited a significant increase intracellularly when compared to cell-surface interactions. These data suggest that the cells may be internalizing C1q via binding with CD44. I then hypothesized that C1q also directly interacts with the intracellular domain of CD44, which is known to cleave and translocate to the nucleus where it can directly modulate gene expression. To test this, I performed additional PLAs probing for C1q interactions with CD44's intracellular domain (ICD). The PLA data confirms that in both microglia and neural stem cells, C1q interacts with the CD44 ICD. CD44 plays various roles in inflammation and gene expression, making C1q-CD44 ICD interactions a compelling therapeutic target. Moreover, elevated levels of C1q in the CNS are associated with aging, neurotrauma, and neurodegeneration; thus these data will inform mechanisms of inflammation and dysregulation across a broad range of disorders.

Poster Presenters - Abstracts

Laura Tennis - #29

Neural Stem and Progenitor Cell (NSPC) differentiation modulates critical aspects of early brain development, and postnatally NSPCs enable brain repair and remodeling. Despite the critical role that NSPCs play in brain generation and regeneration, there is still much we do not understand about how NSPC interactions with the neural niche affect differentiation and in turn neural development. Post-translational modifications of cell-surface proteins and lipids by sugar molecules, or glycans, play a major role in how cells sense and respond to a given environment by affecting the trafficking, mobility, and activity of cell-surface receptors. Previous work in the Flanagan lab found that one type of glycan modification, N-glycan branching, regulates NSPC fate and early brain development in mice. However, the mechanisms by which N-glycan branching modulates NSPC differentiation and neural development remains unknown. Through an initial proteomic screen of NSPC cell-surface proteins, we found that metabolically stimulating the activity of the N-glycan branching enzyme MGAT5 by treatment with its substrate, N-acetylglucosamine (GlcNAc), broadly decreased cell-cell and cell-ECM adhesion molecules, such as integrins α2, α6, and β1 and N-cadherin. From multiple quantitative adhesion assays, we found that GlcNAc's effect on adhesion molecule expression led to decreased cell-cell and cell-ECM adhesion in NSPCS with high N-glycan branching, while decreasing N-glycan branching by MGAT5-KO specifically increased laminin-based adhesion in NSPCs. Such results indicate that integrin-mediated adhesion to laminin may be particularly important to the mechanism by which N-glycan branching regulates NSPC fate. While our data has identified preliminary links between cell surface glycosylation, adhesive interactions, and NSPC fate, it remains unclear what signaling pathways and transcription factors are involved in translating these changes at the cell surface into differences in NSPC fate. We therefore performed SUrface protein Glycan And RNA-sequencing (SUGAR-seq) in order to tie N-glycan branching to signaling events within distinct neural progenitor subpopulations. Our continued analysis of the SUGAR-seq dataset aims to (a) determine N-glycan branching effects on cellular heterogeneity of the NSPC pool, (b) validate N-glycan branching-mediated changes to adhesion modulators, and (c) tie changes in N-glycan branching to signaling events within distinct NSPC subpopulations.

Samir Malhotra - #30

Stem cell-derived retinal organoids (RtOgs) offer a valuable platform for studying human retinal tissue in vitro and hold promise for in vivo transplantation. Addressing challenges of heterogeneous organoid manufacturing methods, we seek to optimize current RtOg protocols through chemical and physical manipulations. Additionally, we demonstrate ongoing tissue development in a microfluidic bioreactor system, providing a controlled environment with continuous media supply.

Organoids were derived from a genetically modified human embryonic stem cell line expressing CRX-GFP (Collin et al., 2016). Two manipulations were tested: Neural Induction Medium with N2 supplement (NIM-N2) and NIM with B27 without retinoic acid supplement (NIM-B27 w/o RA) [Days 0 – 20], and whether 3D-suspended cultures with Matrigel dissolved in media (ultra-low attachment plates) yield more retinal organoids compared to 2D Matrigel-coated cultures. Embryonic body (EB) diameter was assessed on Days 1, 5, and 7 of differentiation. 3D tissue structures from low-attachment plates were categorized on Day 25 and 26 as: retinal, mostly retinal, mostly non-retinal, and non-retinal. Nine retinal organoids were transferred to a polydimethylsiloxane (PDMS) microfluidic bioreactor for long-term culture, with subsequent brightfield and fluorescence imaging taken every week.

Poster Presenters - Abstracts

Pallabi Pal - #31

Inclusion Body Myopathy associated with Paget's disease of the bone, frontotemporal dementia (IBMPFD), and amyotrophic lateral sclerosis (ALS) is a rare syndromic disease caused by gain-of-function variants in the Valosin Containing Protein (VCP) gene. VCP disease variants affect the consolidation of aggregate-prone proteins into inclusion bodies and disrupt the autophagic degradation of ubiquitylated proteins. There is currently no treatment for this progressive disease associated with early demise resulting from proximal limb girdle and respiratory muscle weakness. Antisense Oligonucleotide (ASO) technology has emerged as a powerful direct therapeutic alternative to conventional small molecule approaches or gene replacement strategies for the treatment of genetic disorders. We hypothesize that inhibiting VCP with ASO technology will ameliorate the clinical manifestations of this debilitating disease by normalizing VCP activity, thus improving pathology from the disrupted pathways.

In this study, we assessed the effect of ASOs specifically targeting the human VCP gene in the patient (R155H) iPSC-derived skeletal muscle progenitor cells (SMPCs). ASOs were well tolerated up to 5 μM concentration and significantly reduced VCP mRNA and protein expression by ~ 50%. Additionally, TDP 43 mRNA and protein expression was reduced by 50% and 60 % upon ASO treatment compared to untreated cells.

We then treated the transgenic mouse model of VCP disease which overexpresses the humanized VCP gene with the severe A232E mutation, with weekly subcutaneous injections starting from 6 months of age for 3 months. ASO2 demonstrated tolerability in VCP transgenic mice and showed over 50% knockdown of VCP at the mRNA level and the protein level compared to control ASO. We found improvement in the autophagy markers and reduction in TDP-43 expression, hallmarks of VCP disease. ASO treatment also decreased the number of central nuclei in myofiber in VCPA232E mice as compared to control ASO treatment. ASO2-treated VCP A232E mice showed improvements in motor testing studies including the inverted screen and Rotarod tests compared to mice treated with control ASO. These results targeting VCP in SMPCs and mice with the VCP A232E variant suggest that ASOs targeting VCP could be beneficial in preventing the progression of the myopathy in patients with VCP MSP1.

Emil Lundqvist - #32

In the cardiovascular system, form and function are intricately linked on all length scales. At the cell-level anisotropic patterns of cardiomyocytes help drive the conduction pathways necessary to orchestrate a synchronous contraction; at the organ level, the structure of the atrium and ventricles are specifically tuned to pump blood throughout the body. As the myocardium develops into this complex machine, cardiomyocytes undergo maturation in order to reach the state at which they can circulate blood throughout the human body in perpetuity. Current in vitro research to further understanding of and mimic the native cardiovascular environment is hindered by the limitations of current protocols used to promote human induced pluripotent stem cell-derived cardiomyocytes (hiPSC-CMs) towards high fidelity adult maturation state. Here, we hypothesize that utilizing a materials based delivery of biophysical cues common to the native myocardium, including topographical anisotropy, electrical stimulation, and extracellular matrix compositions will promote hiPSC-CM maturation. Previously established strategies for introducing these biophysical phenomena include extracellular matrix micropatterning, carbon electrodes or electroactive organic materials. Our current work leverages peptide-based materials bearing electroactive π-conjugated segments to influence conduction pathways and cell topography of cardiomyocytes, with the ultimate goal of improving stem cell cardiomyocyte maturation and exploring the impacts of variation in biophysical cues with defined extracellular matrix composition mimicking the dynamic environments in the developing heart.

Poster Presenters - Abstracts

Sujeung Lim - #33

The hierarchical organization of natural peptides can be utilized as a synthetic tool to enable properties in soft biomaterials that are highly reliant on molecular ordering and the formation of nanostructured networks. In this work, I will be presenting the utility of peptides as side chains with tunable noncovalent interactions that can modulate the properties of chromogenic and optoelectronic conjugated polymers, as well as the impact of the resulting bioscaffolds on morphology and behavior of excitable cells such as cardiomyocytes. First, I will discuss how electrostatically driven peptide coassemblies direct the conformational dependent structural order and thermochromic behavior of peptide-functionalized chromogenic polymers (polydiacetylenes, PDAs) under neutral, aqueous environments. A suite of spectroscopic characterization unravels the inherent structural order of model peptide-PDAs that control the chromatic phases that exist during thermochromic cycles. The positively charged peptide-PDA formed a β-sheet-like assembly with higher structural order than its disordered, negatively charged peptide-PDA. The equimolar coassembly resulted in a polymer with a more ordered structure than negatively charged peptide-PDA that still meets the geometric requirement for topochemical polymerization. Although all samples demonstrated thermochromicity, the coassembly experienced the least hysteresis in the aqueous state, and stabilization of the coexistence of blue and red phase chains was observed in the film state. In the latter half of the presentation, the utility of a sequence pair with charge complementarity for directing the order of energy donor and acceptor units to create photocurrent-generating bioscaffolds compatible with cardiac tissues will be shown. The properties of these coassemblies provide important insights on the role of coassembly-driven photoinduced energy transport processes for this biomaterial. Importantly, our coassembled scaffolds can generate photocurrents both as dry films (~2 nA) and under aqueous environments (~12 nA) upon 415 nm illumination. Lastly, these complementary peptide coassemblies were interfaced with cardiomyocytes, whereby their contractility indicates that the cardiac beating rate could follow the frequency of light pulses even without any optogenetic modification on the cells. Currently, we are investigating the effect of the stimulation on iPSC-CMs on control vs. peptides-coassemblies at the molecular level by looking at gene expression and cellular morphology. Ultimately, with these stimulatory peptide-based nanomaterials, we hope to address long-standing challenges in the fidelity of human cardiac tissue models used for high-throughput drug screening or disease modeling.

Sydney Prange - #34

Across many neurodegenerative diseases, including Huntington's disease, amyotrophic lateral sclerosis, Alzheimer's disease, Parkinson's disease, and spinocerebellar ataxias, neurons exhibit several dendrite defects. Notably, these dendrite defects happen in early disease stages and are associated with symptom onset and pathogenesis, long before any mass neuronal death associated with late stages of disease. In my work as a fifth year PhD candidate in the Thompson-Peer lab, I aim to understand how we might take advantage of neurite regeneration pathways to regenerate dendrites lost in the early stages of neurodegenerative disease, and potentially delay or even reverse disease pathogenesis. I have found that injury to a single primary dendrite branch induces a neuroprotective effect underscored by stabilization of the actin cytoskeleton that can delay and sometimes even reverse dendrite degeneration in Drosophila models of neurodegenerative disease. I have also found that the observed neuroprotective response is specific to dendrite injury and not axon injury, indicating that taking advantage of dendrite regeneration pathways in the absence of injury may present a potential therapeutic target for neurodegenerative disease treatment.

Poster Presenters - Abstracts

Austin Silva & Sabrina Calderon - #35

Pancreatic ductal adenocarcinoma (PDAC) is an aggressive malignant disease with a dismal survival rate due to insufficient early diagnosis markers and effective treatment options. The initiation and progression of this disease have been well characterized as a multistep process associated with genetic and epigenetic changes within malignant cells. Here, we focus on UHRF1 (ubiquitin-like with plant homeodomain and ring finger domains 1), a multidomain protein pivotal for maintaining DNA methylation that is known to be overexpressed in PDAC. This overexpression has been implicated in the epigenetic silencing of multiple tumor suppressor genes in pancreatic cancer, thereby playing a significant role in pancreatic oncogenesis. Although previous studies have elucidated UHRF1's role in pancreatic tumorigenesis, the therapeutic potential of targeting UHRF1 remains unknown. To address this gap, we generated pancreatic-specific Uhrf1 knockout mice (Uhrf1PKO) to investigate the impact of UHRF1 loss-of-function on PDAC development and progression. Compared to control mice, Uhrf1PKO mice pancreata exhibited notable abnormalities indicative of disrupted tissue homeostasis, including pancreatic lipomatosis and increased immune infiltration. This disruption of homeostasis was further exacerbated in conjunction with oncogenic mutant Kras, the most commonly found mutation in PDAC and genetic initiator for exocrine neoplasia. Interestingly, Uhrf1PKO mice fail to maintain cancer precursor lesions, highlighting a fundamental role for UHRF1 in the oncogenic transformation of the pancreas, which is known to involve the reactivation of the embryonic transcriptional state. Collectively, this data suggests that UHRF1 loss leads to rewiring of the pancreas parenchyma and immune landscape.

Amanda Tedesco - #36

While there has been much research focused on tendon-to-bone healing with rotator cuff tears, there has been limited understanding of the changes to the muscle. Animal models have shown an age-related muscle stem cell (MuSC) pool depletion and accumulation of inflammation-induced senescent MuSCs that impair regeneration. Yet, there is limited extrapolation to the human condition and no studies have evaluated human MuSC senescence after tendon injury.

With IRB approval, supraspinatus muscle biopsies (n=16) and a subset of ipsilateral deltoid muscle biopsies (n=8) were performed at the time of standard-of-care surgery for patients with confirmed rotator cuff tear. Samples were cryosectioned and immunostained to quantify MuSC density (Pax7+DAPI+ MuSCs/100 MF20+ myofibers) and proportion of p16INK4a+ senescent MuSCs. Sections were also stained to quantify myofiber cross-sectional area (CSA) (MF20, laminin), proportion of slow oxidative fibers (Myh7), fibrosis content (Collagen I/II/III), and fat content (OilRedO). Statistical analyses comparing variables by Goutallier grade and age were performed using unpaired t-tests on Prism GraphPad with significance level set to $p<0.05$.

Poster Presenters - Abstracts

Lan Weiss - #37

Genetically modified adeno-associated virus (AAV)-mediated gene therapies are increasingly utilized, with over a hundred clinical trials underway and several therapies already approved by the Food and Drug Administration (FDA) for patient treatment. Recently, a myotropic AAV variant, AAVmyo, has emerged as a promising vector for delivering gene payloads specifically to muscle tissue.

VCP disease, also known as Multisystem Proteinopathy (MSP1), is a rare inherited disorder caused by mutations in the VCP (Valosin Containing Protein) gene. These pathogenic variants result in hyperactive enzymatic activity, indicative of a gain-of-function mechanism. To address this mechanism of disease, we propose utilizing a single-vector, dual-function approach utilizing AAVmyo. This strategy involves the co-expression of VCP silencing elements alongside rescue vectors to replace endogenous VCP with exogenous functional VCP, offering a targeted and efficient therapeutic solution.

In vitro biopotency assessment of three mirVCP candidates revealed that mirVCP2 achieved significant knockdown of VCP, reducing VCP mRNA by 75% and VCP protein expression by 40% in HEK293T cells. Importantly, codon-optimized wild-type VCP was not targeted by mirVCP2, demonstrating specificity. Ongoing experiments involve testing this approach in VCP patient -derived iPSC skeletal muscle progenitor cells and VCP homozygous mouse model. Similar approaches arebeing applied for related MSP such as Heat Shock Protein B8 (HSPB8) related MSP.

Our proof-of-concept investigations highlight the potential applicability of this knockdown-and- replace strategy for treating a wide range of dominant genetic disorders with gain of function mechanism.

Alyaa Shmara - #38

Heat shock protein family B member 8 (HSPB8) is a chaperone involved in the Chaperone Assisted Selective Autophagy (CASA) complex. HSPB8 in conjunction with BAG3 recognizes and promotes the autophagy-mediated removal of misfolded proteins associated with motor neuron disease including amyotrophic lateral sclerosis (ALS) and spinal and bulbar muscular atrophy (SBMA). Mutations in HSPB8 gene, which has previously been associated with the axonal type of Charcot Marie Tooth, have recently been associated with autosomal dominant rimmed vacuolar myopathy. Affected patients have adult-onset limb girdle myopathy with muscle biopsy showing fatty replacement, endomysial fibrosis, and rimmed vacuoles leading to progressive muscle atrophy and early demise.

We have previously demonstrated reduced expression of HSPB8, disrupted autophagy and TDP-43 in patient fibroblasts and iPSC-derived skeletal muscle progenitor cells (SMPC). There is no treatment available for this debilitating disease, an unmet need which we have tried to address by upregulation of HSPB8 and enhancement of autophagy. High throughput screening identified trehalose, a naturally occurring disaccharide, as a potent HSPB8 inducer and autophagy facilitator.

In this study, we assessed the effect of trehalose in the HSPB8 patient iPSC-derived skeletal muscle progenitor cells (SMPC) Trehalose was well tolerated up to 100 mM concentration. The qPCR and western blot data showed that trehalose induced gradual increase over 48h of the expression of HSPB8, autophagic proteins LC3B and p62, and decrease of TDP-43 expression.

The knock-in Hspb8 mouse model with the c.515dupC fs variant shows significant muscle weakness at 15 months of age. Muscle pathology reveals increased TDP-43, and autophagy pathology recapitulating disease phenotype. We treated 12 to 15-month-old Hspb8 mutant mice in addition to WT littermates with 2% trehalose in drinking water for 4 months and compared motor performance to untreated Hspb8 mutant and WT mice. Preliminary results from behavioral motor testing using rotarod, inverted screen test, and grip strength showed improvement in motor function starting after one month of treatment. Biochemical and histological studies are pending for the effects on typical muscle pathology.

Our preliminary results show promising results from trehalose treatment for HSPB8-associated rimmed vacuolar myopathy and may have potential in related neuromuscular disorders.

Poster Presenters - Abstracts

Ruben Gonzalez - #39

Human tissue-based models serve as crucial intermediate tools to investigate the mechanisms underlying human disease and to validate drugs. Fragile X syndrome (FXS) is among the most prevalent forms of intellectual disability, caused by monogenetic mutation. In FXS patients, hypermethylation at the promoter region of the fragile X mental retardation 1 (FMR1) gene results in reduced or absent expression of fragile X mental retardation protein (FMRP), a multifunctional RNA-binding protein. Recent studies employing FXS cortical organoids have elucidated cellular and molecular mechanisms leading to FXS phenotypes. However, these investigations have lacked interneurons, which are essential for studying FXS phenotypes. The primary objective of this study is to establish the ganglion eminence-cortex (GE-Cx) fusion organoid system as a more accurate model for FXS, incorporating both excitatory and inhibitory neural networks for drug screening and validation. Cortical organoids were generated from FXS patient lines and preliminary findings indicate an increased number of SOX2+ neural progenitors and a reduced count of TBR1+ neurons in D98 FXS organoids, suggesting premature neuronal differentiation. Currently, we are generating FXS GE-Cx fusion organoids to investigate inhibitory neuron migration and alterations in axo-dendritic morphology in interneurons. This alternative human-based model system, the GE-Cx fused organoids offers an unprecedented opportunity to explore FXS excitatory and inhibitory imbalance and would be a better platform for drug validation prior to clinical trials.

Javier Lepe - #40

GBM is a devastating CNS cancer with a median survival of 14.6 months. Less than 50% of patients survive up to 2 years, and less than 1% survive up to 10 years after receiving the current standard of care. Patients diagnosed with GBM undergo surgical resection, chemotherapy with temozolomide, and radiation treatment. However, the current standard of care is ineffective in preventing tumor recurrence, and resistant tumors become difficult to treat as alternative treatment options are limited. Chemotherapy resistance in GBM is attributed to multiple biological mechanisms that ultimately lead to a high incidence of tumor recurrence. These resistance mechanisms involve tumor heterogeneity, glioma stem cells (GSCs), elevated levels of DNA repair enzymes, and mitochondrial reprogramming. Pathways that are important for maintaining stemness in GSCs also drive DNA repair mechanisms which makes them a favorable target for treatment.

Mitochondria Associated Granulocyte Macrophage colony-stimulating factor-Signaling molecules (Magmas) is a 13kDa nuclear coded mitochondrial protein. Magmas is a subunit of the translocase of the inner membrane 23 (TIM23) complex and is an essential regulator of protein trafficking into the mitochondrial matrix. Magmas has been reported to be upregulated in human cancers such as GBM, pituitary adenomas, and prostate cancers. Initial studies have demonstrated that Magmas negatively regulates the stimulatory activity of DNAJC19, a J-protein that stimulates the ATPase activity of mitochondrial heat shock protein 70 (mtHsp70). Magmas is essential for regulating the translocation of precursor proteins needed for mitochondrial biogenesis and homeostasis. We queried Magmas expression from publicly available RNA seq datasets from GBM patients and revealed that Magmas is strongly correlated with the DNA repair enzyme O6-Methylguanine-DNA Methyltransferase (MGMT) and aerobic respiration. Magmas was also found to be significantly upregulated in the proneural GBM subtype, molecular signature of GSCs that reside in the perivascular niche. In addition, we observed significantly elevated levels of Magmas with TMZ treatment and sodium dichloroacetate, indicating that Magmas participates in metabolic reprogramming. We previously reported that pharmacological inhibition of Magmas with BT9 is cytotoxic and significantly decreases oxygen consumption in GBM cells. We now report that BT9 treatment initiates the mitochondria's canonical unfolded protein response (UPR), reduces protein trafficking at the TIM23 pore complex, and increases proteolytic stress. We also report from our in vitro studies that GSCs are sensitized to TMZ when combined with BT9. These findings suggest Magmas plays an essential role in metabolic reprogramming and contributes to TMZ resistance, making it a potential target for clinical translation in glioma.

Poster Presenters - Abstracts

Dahlia Ordaz - #41

The implementation of chemotherapeutic drugs has significantly improved cancer survivorship. These therapeutic advancements have led to observable neurocognitive impairments in patients receiving chemotherapy. These chemotherapy-related cognitive impairments (CRCI), also known as 'chemo-brain' or 'chemo-fog,' are common and often debilitating side effects of these therapeutic drugs. Approximately a third of surviving cancer patients are subjected to the life- altering side effects of chemo-brain. Cisplatin (CIS) is a platinum-based chemotherapeutic drug that inhibits cancer cell division and induces apoptosis. CIS is used to treat a variety of solid cancers, such as ovarian, cervical, head and neck, and gastric cancer. Previous studies have shown that poly (ADP-ribose) polymerase (PARP)1 inhibitors are not only effective cancer treatments, but also display neuroprotective effects and alleviate neuroinflammation in the brain in animal models of degenerative neurological disorders. PARP is involved in various cellular processes, such as maintaining genomic integrity and DNA repair, energy/mitochondrial metabolism, and inflammatory responses. Upon the detection of DNA damage, PARP (and especially PARP1) recognizes these breaks and facilitates DNA repair by recruiting DNA repair machinery to these damaged sites. Niraparib is a brain penetrant, potent and selective PARP1 inhibitor that is approved for maintenance therapy in combination with platinum-based drugs in adults with advanced ovarian cancer. Notably, PARP1 inhibitors have already shown promise in preclinical models of neurodegeneration in patients with Alzheimer's, strokes,
Parkinson's Disease, and multiple sclerosis, due to their ability to dimmish ROS production, and reduce microglial activation. We have previously reported that CIS affects dendritic branching and density in vitro in primary hippocampal neurons (HN). Our current research suggests that CIS also activates PARP in the neural stem cells and HN, and the niraparib pretreatment potentially protect these cells from damage. We, therefore, hypothesize that the PARP1 inhibitor niraparib when administered before CIS might prevent the CIS-induced neuronal and neural stem cell damage and mitigate the cognitive impairment.

Rongruo Zhang - #42

Spinal and bulbar muscular atrophy (SBMA), also known as Kennedy's disease, is a rare X-linked neurodegenerative disorder that affects men. A polyglutamine expansion in the first exon of the androgen receptor (AR) causes progressive muscle weakness and atrophy in the facial, bulbar, and limb muscles. AR is a steroid hormone nuclear receptor that dimerizes upon ligand binding and recruits co-factors to regulate androgen responsive elements. Approximately 50% of SBMA patients exhibit arrhythmia by electrocardiogram, and some patients are susceptible to sudden cardiac arrest. It is not clear whether these cardiac complications are caused by inherent problems with the heart or are a secondary outcome of co-morbidities, including hypertension and diabetes. In this study, we test whether the polyglutamine expansion in AR causes cell-intrinsic problems in cardiomyocytes. We use human induced pluripotent stem cells (iPSCs) bearing polyglutamine expansions in AR to model the disease. Immunostaining of AR in cardiomyocytes differentiated from iPSCs show AR translocation to the nucleus upon treatment with 5α-dihydrotestosterone (DHT), a potent ligand and metabolite of testosterone. We observe differences in cell size and sarcomere density in SBMA cardiomyocytes compared to healthy controls. Calcium imaging reveals that SBMA iPSC-cardiomyocytes are susceptible to arrhythmic events and that this propensity is not dependent on ligand binding. These data demonstrate that mutant AR induces cell-intrinsic problems with calcium handling, suggesting that SBMA patients exhibit arrhythmias due to inherent deficits in cardiac function. This work provides insight into the mechanistic origins of heart complications in SBMA, highlighting the importance of cardiac care for SBMA patients.

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