Combined Degree Program
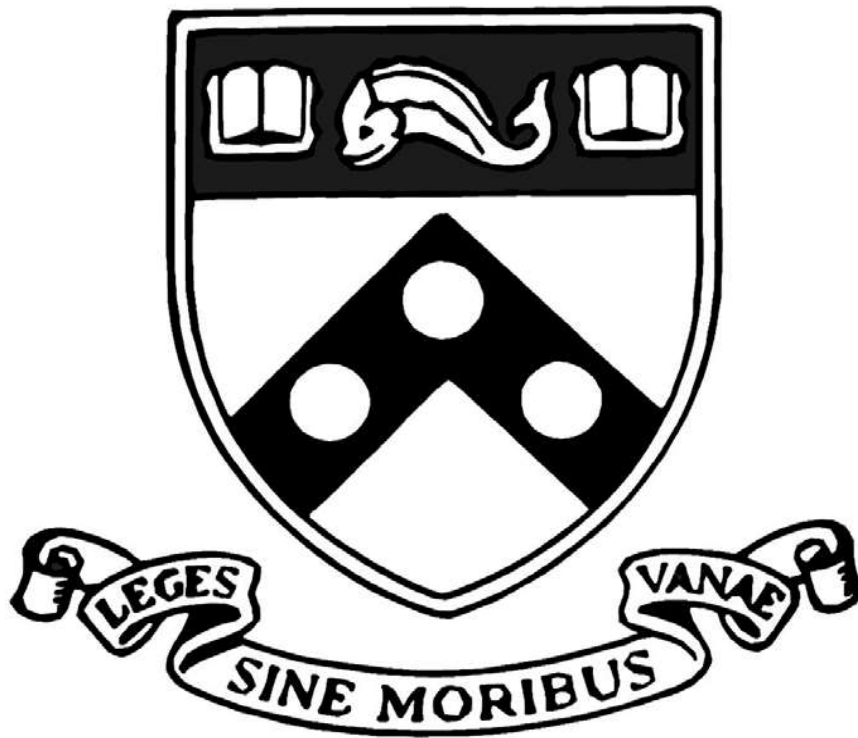# Annual Retreat
(Virtual)

August 6, 2021

Perelman School of Medicine at the University of Pennsylvania

The Combined Degree and Physician Scholar Programs Administration

Skip Brass, MD, PhD   Associate Dean and Director
Rahul Kohli, MD, PhD   Associate Director
Aimee Payne, MD, PhD   Associate Director
Donita Brady, PhD   Steering Cmt Member

Name	Role
Skip Brass, MD, PhD	Associate Dean and Director
Rahul Kohli, MD, PhD	Associate Director
Aimee Payne, MD, PhD	Associate Director
Donita Brady, PhD	Steering Cmt Member
Horace DeLisser, MD	Steering Cmt Member
Robert Heuckeroth, MD, PhD	Steering Cmt Member
Audrey Odom John, MD, PhD	Steering Cmt Member
Mark Kahn, MD	Steering Cmt Member
Max Kelz, MD, PhD	Steering Cmt Member
Erle Robertson, PhD	Steering Cmt Member
Mike Atchison, PhD	Director, VMD-PhD program
Bruce Freedman, VMD, PhD	Steering Cmt Member, VMD-PhD program
Nicola Mason, B Vet Med, PhD, DACVIM	Steering Cmt Member, VMD-PhD program
Michael May, PhD	Steering Cmt Member, VMD-PhD program
Susan Volk, VMD, PhD	Steering Cmt Member, VMD-PhD program
Maggie Krall	Director of Administration
Tiffany Brooks, MBA	Finance and Operations Manager
Maura Tucker, MS.Ed	Associate Director, MD-PhD Program
Francia Portacio, MPH	Associate Director, Physician Scholars
Hope Charney, MA	Program Assistant to Skip Brass
David Bittner, MA	Coordinator, MD-PhD Program
Yong No	Coordinator, VMD-PhD Program

Table of Contents

Welcome to the Retreat —
from the MD-PhD Program Director

Here's to Maggie: The heart and soul of Penn MSTP
July 26, 2021

Some years I feel uncertain about how to best use this space, but this year the decision was easy: 2021 marks the 25th anniversary of Maggie's arrival as administrative director of Penn's MSTP.

I'd like to be able to take the credit for hiring Maggie, but I can't. That decision was made by Glen Gaulton, my predecessor as MSTP director. At the time, Maggiewas a relatively recent graduate of Bryn Mawr College with a B.A. in English *magna cum laude* who was working as a special projects coordinator and student records administrator for BGS (Biomedical Graduate Studies). The job as administrative director (it was called something different back then) for the MSTP fellopen because Liesel Baker, who had held the post for many years, was about to step down. In a remarkable flash of insight, Glen hired Maggie. She arrived just in time to tackle the 5 year competing renewal of our NIGMS MSTP T32 grant. Twenty-five years later and Maggie is still talking about what it felt like going from 0 to 60 mph in 3 seconds.[1] The MD/PhD program was smaller then. There were fewer students and far fewer expectations about what goes into a really effective training program. Mrs. Baker had, however, set a high standard when it came to the program administrator's role in taking care of the students in the program.Maggie has more than sustained that high standard.

A lot has happened to all of us since 1996. Maggie has raised 2 terrific kids at home, while also serving as surrogate parent to hundreds of MSTP students and faculty. We've grown a lot as a training program and as a community of present and future physician-scholars. Through it all, Maggie has stretched and been stretched, almost to the limit, but always with a smile on her face and always with everyone's best interests at heart. She has kept up with us all and usuallybeen ahead of the curve, looking to what lies ahead and not just what is happening now. She'snever been an MD/PhD or VMD/PhD student herself, but she knows the path to be followed atleast as well as any of us who have walked it.

Five years after joining the MSTP, Maggie and our long serving business administrator, Nam Narain, were selected as the joint winners of the 2001 University of Pennsylvania Model of Excellence award for their record of accomplishments in the organization and running of the MSTP. Maggie and Nam had a prominent place in the awards presentation before a large and enthusiastic crowd that filled Irvine Auditorium. Recognition at the university level is hard to come by, but Maggie and Nam deserved it.

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[1] Knowing Glen as I do, I can imagine how the discussion may have gone: "Glad to have you here. By the way, we have this small thing to do…"

In 2012, Maggie was a finalist for the annual Model Supervisor Award from the university - an honor for which she was justifiably proud because the nomination came in part from staff and students who worked for her and with her. That included 3 current and former staff members (Amy Nothelfer, Mary Tiedeman and Maureen Osciak), one of her closest colleagues (Helene Weinberg), who was the med school's registrar at the time, and two of the then-current MD/PhD students, Stephanie Cross and Krishna Vijayendran. Their lengthy nomination packet began: "Maggie Krall exemplifies a model supervisor through her fierce dedication and integrity, professionalism, leadership, guidance, accessibility, compassion and commitment to the university, school, colleagues and her staff." One of the students wrote: "…above all, Maggie is always fair, even if it ends up making her job far harder or requiring more of her time… the well-being of all is considered even when decisions are being made by or for a smaller group." And finally: "After coming here, I realized that a huge reason for the program's reputation and success is due to Maggie Krall."

I couldn't possibly say any of that better. Maggie leads a busy team whom she inspires with her example. She works closely with and is respected by the faculty and staff of the medical education office and Biomedical Graduate Studies. She spends endless hours with students, staff and faculty and still manages to get a huge amount of work done[2] while never forgetting her highest priority: the care and feeding of MSTP trainees. She does it all with aplomb. Maggie is respected nationally within the ranks of the AAMC GREAT Group on medical scientist training for her wisdom and experience. If Penn holds pride of place as the Best MSTP in the Galaxy™, it is in no small part due to Maggie's efforts and commitment. She cares deeply about each and every one of us.

Later this academic year when we can all gather in one place at the same time, we'll meet to honor Maggie in person. Until then, please join me in congratulating and thanking her for 25 years of taking the time to care for all of us. She is the best there is and both a model and friend to us all. We are lucky to have her. She is, as Krishna Vijayendran wrote nearly a decade ago, the heart and soul of Penn MSTP. Welcome everyone to the 2021 Penn MSTP Retreat.

Skip

Skip Brass, MD PhD
Penn MSTP Director and self-identified chair of the Maggie Krall Fan Club

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[2] Often after hours and on the weekend.

Welcome to the Retreat –
from the VMD-PhD Program Director

Welcome to the Penn Combined Degree Retreat!

What a difference a year makes. The transition 17 months ago that sent us into a wild whirlwind and a new normal, seemingly just as rapidly has shifted to something similar, though not identical to the old normal. We are now in a revised normal, and the ability to enter a restaurant now feels absolutely crazy, but what a good crazy. In addition, our nation, institutions, and individuals were confronted by numerous injustices with racial and ethnic injustices top on the list. We can only hope for new understanding on multiple levels to emerge.

I am thankful for all of you and our colleagues for patience and perseverance. Schedules were disrupted, graduations became odd online events, weddings were postponed, children went to school remotely, injustices continued, and tragic illnesses occurred, some resulting in death. It was a year of terrible loss.

As we pick up the pieces of a year like no other, it is also good to soak up some of the positives. Heroic efforts by healthcare providers are to be cherished. Many, many people served sacrificially. We learned that essential personnel include the folks who work in supermarkets, deliver packages, and provide the myriad of services we take for granted. This perhaps should be a point that gives us new perspective and appreciation. We also learned that you really can be in more places than one at the same time. Zoom has certainly changed how I communicate with people all around the world.

I am thankful for the resiliency of many of our students, our faculty, and our institution. In the midst of multiple crises, programs continued. Students graduated and students entered. Students graduating from the VMD-PhD program this year include Robyn Allen, Bailey Baumann, Sondra Calhoun Levigne, and Rebecca Rosenthal. We are incredibly proud of their accomplishments. Entering students this year are Raegan Petch and Josetta Adams. We welcome them to the program and congratulate those graduating.

I hope you enjoy this MSTP retreat day. This is the largest MSTP program in the nation, and the only one that includes veterinary combined degree students. I hope you benefit from and appreciate the advantages of the large critical mass and diversities that our program enjoys.

Welcome again to all current and incoming students.

Sincerely,

Michael Atchison

Many, Many Thanks To the Retreat Planning Committee

We asked the third and fourth year MD-PhD and senior VMD-PhD students to take responsibility for planning this event. They did a fabulous job, and we'd especially like to thank the students who were most active in attending the meetings and organizing.

MD-PhDs

Ryan Boe
Diego Espinoza
Brian Goldspiel
Erin Hollander
Kate Krauss
Casey Lee
Lev Litichevskiy
Graham Lobel
Teddy Steinbock
Matthew Sullivan
Karen Xu

VMD-PhD

Sabina Hlavaty

2021 Incoming Class

MD/PhD

Alexandria Adigun	Cell and Molecular Biology	Howard
Muskaan Aggarwal	Cell and Molecular Biology	MIT
Orlando Arevalo	Cell and Molecular Biology	MIT
Katherine Dorfman	Neuroscience	Brandeis
William Gao	Genomics and Computational Biology	Harvard
Sam Garfinkle	Biochemistry & Molecular Biophysics	Princeton
Angela Gong	Chemistry	Yale
Luiselys Hernandez	Neuroscience	Drexel
Eren Kafadar	Neuroscience	Yale
Sanam Kavari	Cell and Molecular Biology	UNC
Samuel Kim	Immunology	Penn
Rohin Maganti	Pharmacology	Duke
Mattia Mah'moud	Epidemiology and Biostatistics	Harvard
Andrew Nelson	Neuroscience	BYU
Erica Nguyen	Cell and Molecular Biology	Brown
Shreya Parchure	Bioengineering	Penn
Kristen Park	Neuroscience	Hopkins
Cooper Penner	Neuroscience	Brown
Pav Ravindran	Cell and Molecular Biology	Princeton
Kal Shaw	Bioengineering	Princeton
Maryia Svirydava	Immunology	U of Maryland

Saba Tegegne	Immunology	U of Toronto
Henry Utset	Immunology	Vanderbilt
Colin Villarin	Neuroscience	UVM
Chris Wu	Bioengineering	Stanford
Kat Xia	Cell and Molecular Biology	Santa Clara U
Barbara Xiong	Genomics and Computational Biology	Duke
Michael Yao	Bioengineering	Cal Tech
Jack You	Cell and Molecular Biology	Penn

VMD/PhD

Josetta Adams	Immunology	CUNY
Raegan Petch	Cell and Molecular Biology	Colorado State

Graduating Students
and Thesis Information

MD/PhDs

Anthony Angueira
Transcriptional Control and Development of Energy Burning Fat Cells
Thesis Advisor: Dr. Patrick Seale

Hoang Bui Nguyen
Dichotomous engagement of HDAC3 activity governs inflammatory responses
Thesis Advisor: Dr. Mitch Lazar

Ruth Choa
Thymic stromal lymphopoietin induces adipose loss through sebum hypersecretion
Thesis Advisor: Dr. Taku Kambayashi

Eli Cornblath
Network spreading dynamics in cognition and neurodegeneration
Thesis Advisor: Dr. Danielle Bassett

Grant Eilers
Structural and Biochemical Studies of HIV-1 Integration and Inhibition
Thesis Advisors: Drs. Gregory Van Duyne and Frederic Bushman

Benjamin Emert
Uncovering the Origins of Rare-Cell Phenomena
Thesis Advisor: Dr. Arjun Raj

Rafael Jesus Fernandez III
GSK3 Inhibition Rescues Growth and Telomere Dysfunction in Dyskeratosis Congenita IPSC-
Derived Type II Alveolar Epithelial Cells
Thesis Advisor: Dr. Brad Johnson

Sohaib Hashmi
Role of ACTG2 mutations in visceral myopathy
Thesis Advisor: Dr. Robert O. Heuckeroth

Jonathan Lang
Developing Adeno-Associated Viral Vectors as a Gene Editing Platform
Thesis Advisor: Dr. Beverly Davidson

Jeffrey H. Lin
Type 1 conventional dendritic cells are systemically dysregulated early in pancreatic carcinogenesis
Thesis Advisor: Dr. Robert H. Vonderheide

Harrison McAdams
Measuring melanopsin function in humans to understand photophobia in migraine
Thesis Advisor: Dr. Geoffrey Aguirre

Omar Khan
Transcriptional and Epigenetic Regulation of CD8+ T Cell Exhaustion by the Transcription Factor TOX
Thesis Advisor: Dr, E. John Wherry

Nicholas Perkons
Functional Molecular Imaging with DNP-13C-MRSI
Thesis Advisors: Drs. Terence Gade and Mitchell Schnall

Sara Rendell
Closeness Through Distance: The Reformulation of Kinship and Racialized Punishment in U.S. Immigration
Thesis Advisor: Dr. Adriana Petryna

Lee Richman
Dissimilarity to the self-proteome as a novel determinant of immunogenicity
Thesis Advisor: Dr. Robert H. Vonderheide

Alexander Sakers
Identification of a mesenchymal progenitor cell hierarchy in adipose tissue.
Thesis Advisor: Patrick Seale

Eric Sanford
Gene Regulation Displays an Enrichment of Both Additive and Multiplicative Outcomes When Combining the Effects of Two Cell Signals
Thesis Advisor: Dr. Arjun Raj

Sabine Schneider
Novel insights into the genetic and environmental determinants of enteric nervous system biology
Thesis Advisor: Dr. Robert O. Heuckeroth

Annie Toulmin
The Regulation and Function of Major Histocompatibility Complex Class II on Lung Type II Alveolar Cells
Thesis Advisor: Dr. Ike Eisenlohr

Christina Wright
Transcriptional control of enteric nervous system development: insights from mouse models and single-nucleus sequencing
Thesis Advisor: Dr. Robert O. Heuckeroth

Ziyang Xu
Designing Synthetic DNA Encoded Immunotherapeutics and Nanoparticle Vaccines for Enhanced Immune-Mediated Protection
Thesis Advisor: Dr. David B. Weiner

Salina Yuan
Epigenetic Reprogramming in Tumor Plasticity
Thesis Advisor: Dr. Ben Z. Stanger

Di Zhang
Sculpting 3D chromatin folding via genome editing
Thesis Advisor: Dr. Gerd Blobel

Linda Zhou
The 3D Genome as a new dimension in understanding pathologic short tandem repeat instability
Thesis Advisor: Dr. Jennifer E. Phillips-Cremins

2021 MSTP Virtual Retreat
Agenda

*Please note – all sessions will be hosted within the same link via Gather.town
and times are listed in Eastern Daylight Time (EDT)*

August 6, 2021

Opening Remarks
9:00 – 9:15am

Student Talks
9:15 – 10:15am

Ruth Choa
"Sweating fat": Thymic stromal lymphopoietin in immunometabolism and skin immunity

Brinkley Raynor
The impact of the COVID-19 pandemic on rabies reemergence in Latin America: The case of Arequipa, Peru

Daniel Park
High-throughput Oligopaint screen reveals druggable targets that regulate chromatin looping

Lightning Talks
10:15 – 10:35am

Michael Duong
Astrocyte Activation Imaging with 11C-Acetate and Amyloid PET in Mild Cognitive Impairment due to Alzheimer Pathology

Elise Peauroi
The novel innate immune-antagonistic effects of the multifunctional ectromelia virus C15 protein

Eli Cornblath
Computational modeling of tau pathology spread reveals patterns of regional vulnerability and the impact of a genetic risk factor

Kate Krauss
MHC class II on type II alveolar cells modulates type I interferon responses to pulmonary β-coronavirus infection

Alexander Sakers
Defining the lineage of thermogenic perivascular adipose tissue.

Clayton Otter

Investigating the role of MERS-CoV NS4a, NS4b, and nsp15 in evading dsRNA-induced innate immune pathways

Dan Dou

Pathogenic LRRK2 hyperactivity disrupts vesicle transport in the neuronal axon

Philip Hicks

A recombinant vesicular stomatitis virus vaccine platform protects IFNAR deficient mice from lethal SFTSV challenge

Stacy Thomas

A b-Glucan instructs liver macrophages with anti-metastatic activity

Poster Session A
10:35 – 11:05am

Poster Session B
11:05 – 11:35am

Break
11:35 – 11:45am

Keynote Address
11:45 – 12:45pm

Dr. Drew Weissman
Professor of Medicine, University of Pennsylvania

Nucleoside-modified mRNA Therapeutics

Wellness Talks
12:45 – 1:30pm

Kevin Zhang, 6th year
Fantastic (Carnivorous) Plants and Where to Find Them

Skip Brass, MD, PhD and Mark Kahn, MD
Biking Philly: Fast and Slow

Derek Sung, 5th year
Grape Expectations: Choosing YOUR Perfect Wine

Conclusion

Drew Weissman, MD, PhD
Biographical Sketch

Dr. Weissman's laboratory has studied RNA immunity for many years. His lab first identified that mRNA activated dendritic cells and was one of 3 groups that identified that TLR7 and TLR8 recognized RNA. They then went on to identify that the inclusion of modified nucleosides (pseudouridine, 5-Methyl-cytidine, and others) allowed the mRNA to avoid activation of RNA sensors. This allows mRNA delivered in vivo to give very high, up to 1,000-fold, more protein than unmodified mRNA. mRNA, unlike DNA, also has very high transfection efficiency in primary non-dividing cells. These properties allowed us to develop nucleoside-modified mRNA as a transient gene therapy to deliver or replace proteins as a therapeutic. We observed that 10 ng of erythropoietin encoding mRNA resulted in supraphysiologic responses in mice and 1 mg/kg of mAb encoding mRNAs resulted in circulating levels of mAb approaching 600 ug/ml. The combination of the extremely high potency of mRNA encoded proteins due to the amplification by translation and the reduced risks of adverse events as the protein is made by the host's cells has made mRNA therapy a new approach to protein therapeutics. His lab also used nucleoside-modified mRNA to deliver vaccine immunogens in many animal species including: mice, rats, Guinea pigs, rabbits, chickens, and Rhesus and Cynomolgus macaques resulting in potent antibody responses due to the specific induction of T follicular helper cells. They have ongoing interests in developing many vaccines, including COVID-19, pan-coronavirus, hepatitis C, influenza, ebola, CMV, EBV, HIV, dengue, flaviviruses, and others that can quickly move into clinical trials. Additional studies have used modified mRNA for gene editing, as the kinetics of modified mRNA translation are ideal for the delivery of such systems and the targeting of mRNA-LNPs to specific cell types, including lung vascular endothelium, brain, cardiomyocytes, tissue T cells, and bone marrow stem cells.

Wellness Talk Bios

Kevin Zhang, is a 6th-year MD/PhD student planning to pursue a career in ophthalmology or surgery. Hailing from the Philadelphia suburbs, he graduated in 2016 with an AB in molecular biology from Princeton University. He is currently working on his thesis in Dr. Joshua Dunaief's lab, exploring iron-induced lysosomal dysfunction and its role in age-related macular degeneration (AMD). In addition, Kevin is an associate director of communications & special initiatives for the Center for Surgical Health, as well as a Penn Institutional Representative for the American Physician Scientists Association (APSA). Outside these academic interests, Kevin enjoys gardening, fishkeeping, and playing the piano. In particular, he has a passion for growing carnivorous plants, which he has done since third grade, and currently serves as the president of the Mid-Atlantic Carnivorous Plant Society (MACPS).

Dr. Mark Kahn, MD, is a practicing cardiologist in the Division of Cardiovascular Medicine at the University of Pennsylvania. He has won many prestigious awards including the Judah Folkman Award in Vascular Biology from the North American Vascular Biology Organization (NAVBO) and has recently been awarded the Cooper-McLure Chair in Medicine. Mark is widely recognized nationally and internationally for career contributions in the field of vascular development and function. He has made numerous scientific contributions including basic mechanisms of lymphatic vascular function and growth, the role of fluid shear forces in cardiovascular development, and connections between endothelial TLR4, the microbiome in cerebral cavernous malformation. Mark's research has been funded by the National Institutes of Health/National Heart Lung Blood Institutes, the Leducq Foundation and the American Heart Association. Mark has been a mentor to many outstanding graduate students and post doctoral fellows in his laboratory who have become highly successful independent scientists and physician-scientists.

Dr. Skip Brass, MD, PhD, The COVID pandemic kept many of us at home and all of us far more isolated than usual. Finding ways to get out and about safely for exercise and a chance to wrestle with something other than research and patient care became even more important than usual. I used some of my "Wellness for Me" time to explore the Schuylkill River and Perkiomen Creek Valleys on my bike, avoiding traffic by sticking to the trails, listening to audiobooks while I rode, and enjoying nature rather than Nature.

Derek Sung, is a 5th year in CAMB/CPM currently completing his thesis work in Mark Kahn's lab. He is from northern NJ, home to the world's best bagels. He enjoys indoor gardening, RuPaul's Drag Race, karaoke, skincare, and celebrity Architectural Digest home tour videos on YouTube. The craziest thing he's ever done is deciding last minute to go to an Ariana Grande concert in Brooklyn the day before a Cell600 exam that he hadn't studied for.

Student Talks

Ruth Choa
"Sweating fat": Thymic stromal lymphopoietin in immunometabolism and skin immunity
Advisor: Dr. Taku Kambayashi

Brinkley Raynor
The impact of the COVID-19 pandemic on rabies reemergence in Latin America: The case of Arequipa, Peru
Advisor: Dr. Ricardo Castillo

Daniel Park
High-throughput Oligopaint screen reveals druggable targets that regulate chromatin looping
Advisor: Dr. Eric F. Joyce

"Sweating fat": Thymic stromal lymphopoietin in immunometabolism and skin immunity

Ruth Choa, Junichiro Tohyama, Shogo Wada, Hu Meng, Jian Hu, Mariko Okumura, Rebecca M. May, Tanner F. Robertson, Ruth-Anne Langan Pai, Arben Nace, Christian Hopkins, Elizabeth A. Jacobsen, Malay Haldar, Garret A. FitzGerald, Edward M. Behrens, Andy J. Minn, Patrick Seale, George Cotsarelis, Brian Kim, John T. Seykora, Minyao Li, Zoltan Arany, and Taku Kambayashi

Submitted by: Ruth Choa, Immunology
Email: ruth.choa@pennmedicine.upenn.edu
Advisor: Dr. Taku Kambayashi

Obesity is a serious public health concern. Emerging studies indicate that the immune system can regulate weight and energy homeostasis. Here, we show that the cytokine Thymic Stromal Lymphopoietin (TSLP) stimulates T cells to induce selective white adipose loss, which protects against obesity, improves glucose metabolism, and mitigates nonalcoholic steatohepatitis. Surprisingly, adipose loss was not caused by alterations in food intake, nutrient absorption, or energy expenditure. Rather, it was caused by the excessive loss of lipids through the skin as sebum, causing mice to develop a striking "greasy hair" phenotype. Inhibition of sebum secretion or depletion of T cells prevented TSLP-driven adipose loss. TSLP-driven white fat loss and sebum hypersecretion were both mediated via the direct activation of CD4$^+$ or CD8$^+$ T cells through the TSLP receptor in an antigen-independent manner, and these T cells could be seen infiltrating skin sebaceous glands. Furthermore, we found that TSLP and T cells regulated sebum release and sebum-associated anti-microbial peptide expression in the skin at steady-state. In human skin, TSLP expression also correlated directly with sebum-associated gene expression. Together, our study establishes a paradigm in which adipose loss can be achieved by sebum hypersecretion and reveals a previously unknown role of adaptive immunity in skin barrier function through the regulation of sebum secretion.

The impact of the COVID-19 pandemic on rabies reemergence in Latin America: The case of Arequipa, Peru

Brinkley Raynor, Elvis W. Díaz, Julianna Shinnick, Edith Zegarra, Ynes Monroy, Claudia Mena, Michaela De la Puente-León, Michael Z. Levy, Ricardo Castillo-Neyra

Submitted by: Brinkley Raynor, Epidemiology and Biostatistics
Email: bhraynor@vet.upenn.edu
Advisor: Dr. Ricardo Castillo

Canine rabies remains endemic in several areas in Latin America, though there has been enormous progress towards controlling this deadly, zoonotic disease in the past decades. The progress made by these control programs have been disrupted by the COVID-19 pandemic; movement restrictions, stay-at-home orders, and diverted funds have hampered public health officials capacity to conduct rabies surveillance, respond to reports of rabid dogs, and administer mass dog rabies vaccination campaigns. To explore the impact of disruptions caused by COVID-19, we constructed a deterministic, compartment model examining canine rabies dynamics in the city of Arequipa, Peru. We parameterized the model based on 5 years of longitudinal data of the city's dog population, as well as the local rabies incidence data. Due to the low surveillance and vaccination coverage during the year of 2020, we predicted a rise in canine rabies cases as early as the beginning of 2021. Arequipa surveillance data from January to March 2021 confirmed rising trends in reports of canine rabies as well as geographic expansion of canine rabies to a neighboring province. Even with increased COVID-19 vaccination roll-out worldwide, COVID-19 remains a pressing problem in the immediate future; innovative solutions to maintaining public health programs, such as canine rabies control programs in Latin America, in the face of a pandemic are desperately needed as previously under control diseases resurge due to this period of neglect.

High-throughput Oligopaint screen reveals druggable targets that regulate chromatin looping

Daniel S. Park, Son C. Nguyen, Randi Isenhart, Wonho Kim, Aditi Chandra, Jailynn Harke, Jennifer M. Luppino, Yemin Lan, Parisha P. Shah, Rebecca Yunker, May Wai, Patrick Walsh, Sora Yoon, Golnaz Vahedi, Rajan Jain, Eric F. Joyce

Submitted by: Daniel S. Park, Cell and Molecular Biology – Genetics and Epigenetics
Email: Daniel.park@pennmedicine.upenn.edu
Advisor: Dr. Eric F. Joyce

The cohesin complex regulates chromatin organization at the level of topologically associated domains (TADs) and chromatin loops. Mutations in genes encoding for cohesin subunits or its cofactors dysregulates this process and is associated with several disorders termed cohesinopathies. Our understanding of chromatin organization and its function is limited in part, however, by the paucity of factors known to participate in these processes. To discover novel chromatin folding factors, we developed high-throughput DNA or RNA labeling by Oligopaints (HIDRO). This method utilizes high-efficiency Oligopaint fluorescence in situ hybridization (FISH) probes to allow massively parallel DNA FISH. Previously we found that the spatial overlap between adjacent TADs labeled with Oligopaints could quantify the strength of the intervening boundary. We also found that cohesin depletion strengthens boundaries while depletion of the cohesin release factor WAPL weakens boundaries. Using this assay, we conducted an RNAi screen of 3,083 genes for novel regulators of TAD boundary strength. We isolated 24 novel chromatin folding factors associated with three distinct pathways: ubiquitin ligation, calcium signaling, and GSK3 signaling. We have further validated the GSK3A kinase by chemical inhibition and found that its depletion alters the localization of cohesin and, by Hi-C, leads to increased inter-TAD interactions. We also observed a corresponding loss and gain of chromatin loops with an overall increase in average loop length. Finally, chemical inhibition of GSK3A partially rescues the architectural effects of cohesin depletion. GSK3A is novel chromatin folding factor that restricts cohesin activity, and GSK3A inhibition has intriguing therapeutic potential for cohesinopathies.

Poster Session A

Bioengineering

Poster 1A

[Abstract](#)

A normative atlas of intracranial EEG activity and connectivity identifies the seizure onset zone in focal epilepsy
Presenter: John Bernabei | Advisor: Dr. Brian Litt

Poster 2A

[Abstract](#)

Astrocyte Activation Imaging with 11C-Acetate and Amyloid PET in Mild Cognitive Impairment due to Alzheimer Pathology
Presenter: Michael Duong | Advisor: Dr. Ilya M. Nasrallah and David A. Wolk

Poster 3A

[Abstract](#)

Extracellular vesicle liquid biopsy to improve breast cancer screening accuracy
Presenter: Griffin Spychalski | Advisor: Dr. David Issadore

Cell and Molecular Biology

Cancer Biology

Poster 4A

[Abstract](#)

Pancreatic ductal adenocarcinoma growth suppression through loss of Mgat5-mediated N-linked complex glycosylation
Presenter: Erin Hollander | Advisor: Dr. Ben Stanger

Genetics and Epigenetics

Poster 5A

[Abstract](#)

Uncorrelated allelic expression suggests transcriptional parameters that create a barrier for propagating expression variability
Presenter: Ryan Boe | Advisor: Dr. Arjun Raj

Poster 6A

[Abstract](#)

Changes in chromatin accessibility is not concordant with gene expression changes in MCF-7 cells
Presenter: Karun Kiani | Advisor: Dr. Arjun Raj

Poster 7A

[Abstract](#)

High-throughput Oligopaint screen reveals druggable targets that regulate chromatin looping
Presenter: Daniel Park | Advisor: Dr. Eric F. Joyce

Microbiology, Virology and Parasitology

Poster 8A

[Abstract](#)

A novel system for tracking CD4+ T cell responses to Cryptosporidium reveals a requirement for type 1 conventional dendritic cells.
Presenter: Ian Cohn | Advisors: Drs. Christopher Hunter and Boris Striepen

Poster 9A

[Abstract](#)

Investigating the role of MERS-CoV NS4a, NS4b, and nsp15 in evading dsRNA-induced innate immune pathways
Presenter: Clayton Otter | Advisor: Dr. Susan Weiss

Poster 10A

[Abstract](#)

Ubiquitin Ligase SMURF2 Interacts with Filovirus VP40 and Promotes Egress of VP40 VLPs
Presenter: Ariel Shepley-McTaggart | Advisor: Dr. Ronald N. Harty

Genomics & Computational Biology

Poster 11A

[Abstract](#)

Interactions between aging, dietary restriction, and the gut microbiome
Presenter: Lev Litichevskiy | Advisors: Drs. Christoph Thaiss and Mingyao Li

Immunology

Poster 12A

[Abstract](#)

MHC class II on type II alveolar cells modulates type I interferon responses to pulmonary β-coronavirus infection
Presenter: Kathleen Krauss | Advisor: Dr. Laurence Eisenlohr

Poster 13A

[Abstract](#)

A b-Glucan instructs liver macrophages with anti-metastatic activity
Presenter: Stacy Thomas | Advisor: Dr. Gregory L. Beatty

Neuroscience

Poster 14A

Abstract

Computational modeling of tau pathology spread reveals patterns of regional vulnerability and the impact of a genetic risk factor
Presenter: Eli Cornblath | Advisor: Dr. Danielle S. Bassett

Poster 15A

Abstract

Establishing the role of the lateral habenula in central itch processing
Presenter: Suna Cranfill | Advisor: Dr. Wenqin Luo

Poster 1A | Bioengineering

A normative atlas of intracranial EEG activity and connectivity identifies the seizure onset zone in focal epilepsy

John M. Bernabei, Nishant Sinha, T. Campbell Arnold, Erin Conrad, Ian Ong, Joel M. Stein, Russell T. Shinohara, Timothy H. Lucas, Danielle S. Bassett, Kathryn A. Davis, Brian Litt

Submitted by: John Bernabei, Bioengineering
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Advisor: Dr. Brian Litt

Recording seizures using intracranial EEG (iEEG) is an essential tool for surgical planning for patients with refractory epilepsy. Quantitative measures of interictal iEEG are potentially appealing biomarkers, however their utility is limited by the sparsity electrode implantation as well as the confounds of normal neural activity and connectivity which vary spatiotemporally. We propose that leveraging a large number of patients to construct a normative atlas of intracranial EEG activity and connectivity will allow us to reliably map abnormal regions, thereby serving as a tool to increase our understanding of epilepsy and identify better targets for epilepsy surgery. We aggregated interictal iEEG retrospectively across 166 subjects comprising >5000 channels. For each channel, we calculated normalized spectral power and coherence in each canonical frequency band. We constructed an iEEG atlas by mapping the distribution of each feature across the brain, and test the atlas by generating a Z-score for each channel of novel patients. This procedure can reliably identify quantitative abnormalities in clinically relevant areas such as the seizure onset zone (SOZ) and irritative zone. We show that for SOZ within the mesial temporal lobe, measures of connectivity abnormality provide greater distinguishing value than univariate measures of abnormal neural activity. We also find that patients with a longer diagnosis of epilepsy have greater abnormalities in connectivity. We input the Z-scores of each metric to a random forest classifier to determine whether channels are likely to be in the SOZ. By integrating measures of both single-channel activity and inter-regional functional connectivity, we find a better accuracy in predicting the SOZ versus normal brain (area under the curve = 0.78) compared to either group of features alone. The findings of this study serve to directly increase our understanding of the relationship between abnormal neural activity, connectivity and epilepsy, and our methods establish a framework for leveraging big data in surgical planning.

Poster 2A | Bioengineering

**Astrocyte Activation Imaging with ^{11}C-Acetate and Amyloid
PET in Mild Cognitive Impairment due to Alzheimer Pathology**

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Jenny Cai, Arun Pilania, David A. Wolk, Ilya M. Nasrallah**

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Neuroinflammation is a well-known feature of early Alzheimer disease (AD) and Mild Cognitive Impairment (MCI) yet astrocyte activation in response to amyloid plaque pathology has not been extensively evaluated with *in vivo* imaging. Unlike neurons, astrocytes metabolize acetate, which has potential as a glial biomarker of neurodegeneration in response to AD pathologic features. Since the medial temporal lobe (MTL) is a hotspot for AD neurodegeneration and inflammation, we assessed astrocyte activity in the MTL and compared to amyloid and cognition.

We evaluated spatial patterns of *in vivo* astrocyte activation and their relationships to amyloid deposition and cognition in a cross-sectional pilot study of six participants with MCI and five cognitively normal (CN) participants. We measured ^{11}C-acetate and ^{18}F-florbetaben amyloid standardized uptake values ratios (SUVRs) and kinetic flux compared to cerebellum on positron emission tomography (PET), with magnetic resonance imaging and neurocognitive testing.

MTL ^{11}C-acetate SUVR was significantly elevated in MCI compared to CN participants ($P = 0.03$; Cohen $d = 1.76$). Moreover, MTL ^{11}C-acetate SUVR displayed significant associations with global and regional amyloid burden in MCI. Greater MTL ^{11}C-acetate retention was significantly related with worse neurocognitive measures including the Montreal Cognitive Assessment ($P = 0.001$), Word List Recall memory ($P = 0.03$), Boston Naming Test ($P = 0.04$) and Trails B test ($P = 0.04$).

While further validation is required, this exploratory study suggests a potential role for ^{11}C-acetate PET as a neuroinflammatory biomarker in MCI and early AD to provide clinical and translational insights into astrocyte activation as a pathological response to amyloid.

Poster 3A | Bioengineering

Extracellular vesicle liquid biopsy to improve breast cancer screening accuracy

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Breast cancer mortality has decreased by approximately 33% since 1990 due to advances in screening mammography and early detection of cancer. However, women who undergo diagnostic mammography and ultrasound are commonly identified as having BI-RADS category 4 lesions, which corresponds to a likelihood of malignancy between 2% and 95%. We seek to create a non-invasive liquid biopsy to improve the accuracy of assessing likelihood of malignancy for patients with BI-RADS category 4 lesions. In this study, we will apply an immunomagnetic nanofluidic chip to isolate breast cancer-derived extracellular vesicles from plasma; we will analyze the miRNA contents of captured vesicles to identify transcriptional signatures that can classify breast cancer patients. Here, we quantified surface proteins on vesicles isolated from BT-474 breast cancer cell conditioned media using an ELISA, which identified EpCAM and CD24 as candidate surface proteins for immunomagnetically labeling breast cancer-derived vesicles. We will evaluate the labeling of breast cancer-derived vesicles with either anti-EpCAM or anti-CD24 to capture breast-cancer derived vesicles from BT-474 conditioned media spiked into healthy plasma background. After identifying the optimal labeling approach, we will isolate vesicles from plasma of patients with either malignant or benign lesions originally classified as BI-RADS category 4. We will profile the miRNA contents of the captured vesicles and apply machine learning to generate a panel of miRNAs that differentiate malignant samples. Finally, we will validate our assay by determining the accuracy of classifying malignant vs benign samples from a blinded test set.

Poster 4A | Cell and Molecular Biology - Cancer Biology

**Pancreatic ductal adenocarcinoma growth suppression
through loss of Mgat5-mediated N-linked complex glycosylation**

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Pancreatic ductal adenocarcinoma is currently the third leading cause of cancer-related death in the United States. The five-year survival rate of less than nine percent is attributed mainly to a difficulty in early detection and a lack of effective treatments. One potential therapeutic target is tumor-associated glycans. Aberrant glycosylation is a hallmark of cancer, with changed glycosylation patterns found to be involved in many aspects of cancer formation and invasion. The glycosyltransferase MGAT5 catalyzes the formation of β1,6-N-acetylglucosamine branched glycans. Multiple cancers have been found to have increased MGAT5 activity, with overexpression of the enzyme associated with tumor formation, epithelial-mesenchymal transition, and invasiveness.

Using a mouse model ("KPCY") of pancreatic cancer, our lab has demonstrated that clones derived from primary KPCY tumors can be divided into "T-cell-inflamed" or "non-T-cell-inflamed" phenotypes. Normally, T-cell-inflamed lines grow effectively in immunocompetent mice. Knockout of MGAT5, however, allows for complete clearance of tumors. There is no growth deficiency observed when the cells are grown *in vitro*. The phenotype was found to be dependent upon CD4/CD8 T cells, which is supported by the observation that knockout of MGAT5 in non-T-cell-inflamed lines leads to decreased tumor growth rather than full tumor clearance. Mice which have previously cleared MGAT5 knockout tumors, when challenged with the parental T-cell-inflamed line, are now able to clear the parental line. This suggests that when MGAT5 is lost, a tumor antigen is revealed which the immune system can efficiently target and form an immunological memory against.

Poster 5A | Cell and Molecular Biology - Genetics & Epigenetics

Uncorrelated allelic expression suggests transcriptional parameters that create a barrier for propagating expression variability

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Gene expression in individual cells substantially deviates from the population average. This deviation is often referred to as 'noise' and has been found to be an important driver of development and adaptation. In synthetic circuits of bacteria and yeast, the noise in an upstream gene is amplified and propagated to downstream genes. However, the same noise propagation and amplification seems to be absent from higher eukaryotes. Though more complicated means to prevent noise propagation such transcription-factor dimerization have been identified in individual cases, it is unknown whether a minimal model of transcription fit to realistic parameters could also prevent noise propagation, thus providing a universal mechanism to prevent noise propagation. Our work uses allele-specific single-cell RNAseq data to fit parameters for a leaky-telegraph model of transcription. We find that parameters which fit the model to the observed data also give rise to gene networks which do not propagate noise and that network configurations which transmit noise are unstable. Further, we show that these 'tuned' gene networks use a low-pass filter such that they are unresponsive to short fluctuations of noise but remain responsive to longer fluctuations. Finally, we show that there is an inherent trade-off in fluctuation response time and ability to filter noise. Our findings suggest that a minimal model of transcription is sufficient to prevent noise propagation, but that the parameters must be tuned to a narrow region of parameter space.

Poster 6A | Cell and Molecular Biology - Genetics & Epigenetics

Changes in chromatin accessibility is not concordant with gene expression changes in MCF-7 cells

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The relative accessibility of chromatin is an important point of regulation for eukaryotic transcription. It is commonly believed that chromatin accessibility as measured by assay for transposase-accessible chromatin and sequencing (ATAC-seq) is highly correlated with gene expression changes, however this has not been rigorously tested. Here, we use a data set of matched bulk RNA-seq and ATAC-seq in MCF-7 adenocarcinoma cells to investigate the relationship between accessibility of chromatin and gene expression. We further leverage the fact that these cells were exposed to multiple doses of two potent transcriptional modulators, retinoic acid (RA) and tumor growth factor beta (TGF-β) to examine how the relationship between chromatin accessibility and gene expression changes with increasing dose of signal. Overall we found that the degree of concordance between accessibility and expression to be quite minimal even for genes that are the most differentially expressed between ethanol control and high dose signal, indicating that in these signaling pathways accessibility is a poor predictor of changes in expression.

Poster 7A | Cell and Molecular Biology - Genetics & Epigenetics

High-throughput Oligopaint screen reveals druggable targets that regulate chromatin looping

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The cohesin complex regulates chromatin organization at the level of topologically associated domains (TADs) and chromatin loops. Mutations in genes encoding for cohesin subunits or its cofactors dysregulates this process and is associated with several disorders termed cohesinopathies. Our understanding of chromatin organization and its function is limited in part, however, by the paucity of factors known to participate in these processes. To discover novel chromatin folding factors, we developed high-throughput DNA or RNA labeling by Oligopaints (HIDRO). This method utilizes high-efficiency Oligopaint fluorescence in situ hybridization (FISH) probes to allow massively parallel DNA FISH. Previously we found that the spatial overlap between adjacent TADs labeled with Oligopaints could quantify the strength of the intervening boundary. We also found that cohesin depletion strengthens boundaries while depletion of the cohesin release factor WAPL weakens boundaries. Using this assay, we conducted an RNAi screen of 3,083 genes for novel regulators of TAD boundary strength. We isolated 24 novel chromatin folding factors associated with three distinct pathways: ubiquitin ligation, calcium signaling, and GSK3 signaling. We have further validated the GSK3A kinase by chemical inhibition and found that its depletion alters the localization of cohesin and, by Hi-C, leads to increased inter-TAD interactions. We also observed a corresponding loss and gain of chromatin loops with an overall increase in average loop length. Finally, chemical inhibition of GSK3A partially rescues the architectural effects of cohesin depletion. GSK3A is novel chromatin folding factor that restricts cohesin activity, and GSK3A inhibition has intriguing therapeutic potential for cohesinopathies.

Poster 8A | Cell and Molecular Biology – Microbiology, Virology and Parasitology

A novel system for tracking CD4+ T cell responses to *Cryptosporidium* reveals a requirement for type 1 conventional dendritic cells.

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Protective immunity to the intestinal parasite *Cryptosporidium* requires CD4+ T cells, and individuals with defects in CD4+ T cell function can remain chronically infected and diarrheal disease can be life-threatening. The ability to analyze the CD4+ responses to this parasite have been limited, as no MHCII-restricted antigens have been identified. In addition, most of the CD4+ T cells in the gut possess an "activated but resting" phenotype," thus previous studies have not tracked *Cryptosporidium*-specific T cells. To address this, I used CRISPR/Cas9 to generate *Cryptosporidium parvum* expressing the 2W1S and LCMV-gp$_{61-80}$ (gp61) model antigens tagged onto the parasite protein MEDLE2 which is secreted into infected cells. This now allows for the analysis of *Cryptosporidium*-specific CD4+ T cells by utilizing tetramers to endogenous T cells (2W1S) or TCR-transgenic mice (gp61). I have measured parasite-specific CD4+ T cells in the draining mesenteric lymph node, Peyer's patches, small intestine lamina propria, and the epithelium in infected mice using both of these antigens. In addition, while type 1 conventional dendritic cells (cDC1) are linked to the activation of CD8+ T cells, using these transgenic parasites revealed that mice that lack cDC1s were unable to generate parasite-specific CD4+ T cells. This tool now allows further investigation of the antigen presenting cells participating in CD4+ T cell priming, and the functions of CD4+ T cells required for resistance to *Cryptosporidium*.

Poster 9A | Cell and Molecular Biology – Microbiology, Virology and Parasitology

Investigating the role of MERS-CoV NS4a, NS4b, and nsp15 in evading dsRNA-induced innate immune pathways

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MERS-CoV is one of three highly pathogenic coronaviruses (CoVs) that have emerged and caused public health emergencies in the past 20 years. Like other respiratory viruses, MERS-CoV enters the respiratory tract and establishes an infection in the respiratory epithelium, where it encounters host innate immune defenses. All CoVs produce double-stranded RNA (dsRNA) as a byproduct of their replication, and this intermediate can induce three host innate immune pathways: interferon (IFN) signaling, protein kinase R (PKR), and the OAS/RNaseL system. We have previously shown MERS-CoV does not significantly activate these dsRNA-induced pathways. Here, we examine the role of 3 MERS-CoV-encoded innate immune antagonist proteins: NS4a (dsRNA binding protein), NS4b (RNaseL antagonist), and nsp15 (contains an endoribonuclease domain that reduces dsRNA accumulation). Using a BAC-based recombination system, we have generated MERS-CoV mutants lacking these innate antagonists. We show that a MERS-CoV double mutant defective in both NS4a and nsp15 results in significantly increased antiviral IFN induction and activation of PKR compared to either wild-type virus or single antagonist viral mutants. Similarly, an NS4b/nsp15 double mutant significantly activates IFN and RNaseL compared to WT or single mutants. We also observe a log-scale replication defect in these double mutant recombinants compared to WT virus. These findings highlight the importance of dsRNA-induced pathways in limiting MERS-CoV replication as well as the multi-pronged mechanism through which MERS-CoV adeptly evades these pathways. Recent work with primary nasal epithelial cultures has also revealed the physiologic relevance of immune evasion by MERS-CoV. Understanding immune evasion by viruses such as MERS-CoV is critically important, as additional pathogenic CoVs are likely to emerge in the future.

Poster 10A | Cell and Molecular Biology – Microbiology, Virology and Parasitology

Ubiquitin Ligase SMURF2 Interacts with Filovirus VP40 and Promotes Egress of VP40 VLPs

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Filoviruses Ebola (EBOV) and Marburg (MARV) are devastating high-priority pathogens capable of causing explosive outbreaks with high mortality rates. The matrix proteins of EBOV and MARV, called eVP40 and mVP40, respectively, are the key viral proteins that drive virus assembly and egress and VP40 can bud independently from cells in the form of virus-like particles (VLPs). The matrix proteins utilize proline-rich Late (L) domain motifs (e.g., PPxY) to hijack specific host proteins that contain WW domains, such as the HECT family E3 ligases, to facilitate the last step of virus-cell separation. We identified E3 ubiquitin ligase Smad Ubiquitin Regulatory Factor 2 (SMURF2) as a novel interactor with VP40 that positively regulates VP40 VLP release. Our results show that eVP40 and mVP40 interact with the three WW domains of SMURF2 via their PPxY motifs. We provide evidence that the eVP40-SMURF2 interaction is functional as the expression of SMURF2 positively regulates VLP egress, while siRNA knockdown of endogenous SMURF2 decreases VLP budding compared to controls. In sum, our identification of novel interactor SMURF2 adds to the growing list of key host proteins that can regulate PPxY-mediated egress of VP40 VLPs. A more comprehensive understanding of the modular interplay between filovirus VP40 and host proteins may lead to the development of new therapies to combat these deadly infections.

Poster 11A | Genomics and Computational Biology

Interactions between aging, dietary restriction, and the gut microbiome

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The most prevalent diseases—including cardiovascular disease, cancer, and neurodegeneration—are associated with advanced age. Delaying or reversing the mechanisms of aging may therefore also delay the onset of these common and devastating diseases. Although the mechanisms of aging remain poorly understood, an increasingly intriguing hypothesis is that the gut microbiome is intimately related to the aging process. Notably, dietary restriction (DR)—one of the few known ways to reliably and robustly extend lifespan—appears to exert its beneficial effects via the gut microbiome. In order to unravel the interactions between aging, DR, and the gut microbiome, we performed a large-scale experiment in Diversity Outbred (DO) mice, whose genetic heterogeneity better resembles that of humans compared to inbred mice. At six months of age, 960 DO mice were randomized to one of five dietary groups: control (*ad libitum* diet), two caloric restriction groups (20% or 40% fewer daily calories), and two fasting groups (one or two days of fasting per week). Stool samples and extensive aging-associated phenotypes were collected from these mice every six months. We profiled the gut microbiome via metagenomic sequencing of stool samples. Preliminary analysis of this dataset has revealed decreased alpha diversity with age, increased microbiome uniqueness with age, and identification of microbes whose abundance changes with age. Future analyses will focus on diet-associated microbiome changes. This study will be the first longitudinal catalog of aging-associated microbiome changes and the first to extensively compare microbiome changes in different types of DR. Insights gained from this study will contribute to the development of novel lifespan-extending therapies that are more targeted and less onerous than lifelong DR.y

Poster 12A | Immunology

MHC class II on type II alveolar cells modulates type I interferon responses to pulmonary β-coronavirus infection

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The type I interferon (IFN-I) response is a powerful signaling cascade, long recognized as a key contributor to antiviral immunity. However, IFN-I also contributes to immunopathology during viral infections. This dual action means that regulation of the IFN-I response is critical.

Class II major histocompatibility complex (MHCII) is best known for its role in presenting antigen to T cells. However, in this study, we propose an alternate role for MHCII, as a regulator of IFN-I signaling. MHCII is constitutively expressed on type 2 alveolar cells (AT2s); when we selectively ablated MHCII on AT2s in mice (AT2^{MHCII-}), we found that they lost less weight after being infected with the natural mouse β-coronavirus murine hepatitis virus 1 (MHV-1). AT2^{MHCII-} mice also had lower levels of IFNβ (p=0.0425) in their lungs at 2 dpi. However, AT2^{MHCII-} mice show no difference in viral burden in their lungs at the same time point.

From these data, we have constructed a model wherein AT2 MHCII acts as a positive regulator of IFN-I production. Since most IFN-I released in response to *in vivo* infection is produced by plasmacytoid dendritic cells (pDCs), our model proposes AT2s provoke pDCs to release more IFN-I. We propose this regulation occurs via signaling through lymphocyte-activation gene 3 (LAG3), a CD4 analog which serves as an alternate coreceptor for MHCII and is expressed on pDCs. Further investigation of this signaling axis could lead to improved understanding of the regulation of IFN-I signaling and therefore symptom burden in pulmonary viral infections.

Poster 13A | Immunology

A β-Glucan instructs liver macrophages with anti-metastatic activity

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Pancreatic ductal adenocarcinoma (PDAC) has one of the worst 5 year survival rates of all human cancers: a mere 10% in the United States. For most patients, metastatic disease is the main cause of mortality with the liver being the most common site of metastasis. Our previous work demonstrated that a primary pancreatic tumor triggers production of soluble factors, which instruct the formation of a pro-metastatic niche in the liver. Macrophages are a predominant component of this liver niche, yet their role in regulating metastasis remains ill-defined. My data suggest that, in the absence of a niche, liver macrophages do not restrict or promote tumor cell seeding in the liver. In contrast, published data shows that liver macrophages can promote tumor outgrowth once seeding has already occurred. Together, these findings imply that macrophage biology is pliable and thus might be exploited to fight cancer. Inducing "trained immunity" using molecules like β-glucans can alter macrophage biology. Trained immunity involves epigenetic and metabolic reprogramming of innate immune cells so they have an enhanced response to subsequent stimuli. My data show, that β-glucans bind liver macrophages and inhibit liver metastasis. This inhibition is dependent on phagocytic cells, which include macrophages. Together, these findings suggest that myeloid agonists, such as β-glucans, may be able to engender macrophages with the ability to restrict liver metastasis. Future work aims to elucidate the roles of distinct liver macrophage subsets, including Kupffer cells and bone marrow derived macrophages, in the anti-metastatic activity of β-glucans.

Poster 14A | Neuroscience

Computational modeling of tau pathology spread reveals patterns of regional vulnerability and the impact of a genetic risk factor

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Neuropathological staging studies have suggested that tau pathology spreads through the brain in Alzheimer's disease (AD) and other tauopathies, but it is unclear how neuroanatomical connections, spatial proximity, and regional vulnerability contribute. In this study, we seed tau pathology in the brains of nontransgenic mice with AD tau and quantify pathology development over 9 months in 134 brain regions. Network modeling of pathology progression shows that diffusion through the connectome is the best predictor of tau pathology patterns. Further, deviations from pure neuroanatomical spread are used to estimate regional vulnerability to tau pathology and identify related gene expression patterns. Last, we show that pathology spread is altered in mice harboring a mutation in leucine-rich repeat kinase 2. While tau pathology spread is still constrained by anatomical connectivity in these mice, it spreads preferentially in a retrograde direction. This study provides a framework for understanding neuropathological progression in tauopathies.

Poster 15A | Neuroscience

Establishing the role of the lateral habenula in central itch processing

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Itch is a complex sensory experience that also encompasses affective and behavioral components, as evidenced by the common presentation of comorbid depression, anxiety, and other psychological disorders in chronic itch patients. However, the cellular and circuit mechanisms linking pathological itch to affective disorders are poorly understood. Here, we identified a novel role for the lateral habenula (LHb), a predominantly glutamatergic brain region important for negative valence, aversive and avoidance behaviors, and depression, in mediating acute itch behavior. Using c-Fos immunohistochemistry in mice, we found that the LHb is highly activated by both itch and pain stimuli. To genetically access itch-activated LHb neurons, we used the *TRAP2* driver line ($Fos^{iCreERT2}$), which allows permanent expression of a Cre-dependent reporter allele in neurons activated by itch stimulation during a restricted time window. Anterograde tracing of itch-activated LHb neurons revealed projections to both the rostromedial tegmental nucleus and the dorsal raphe nuclei. Using optogenetic and chemogenetic approaches to reactivate itch-activated LHb neurons, we found that this population suppresses active behavioral responses to itch stimulation, such as scratching, and promotes passive immobility. Moreover, activation of these neurons or global chemogenetic inhibition of LHb neurons (using the $Vglut2^{Cre}$ driver line) did not affect general locomotion, suggesting that the itch-evoked immobility behavioral response is context-specific. Activation also did not affect pain-related behaviors, raising the possibility that discrete LHb ensembles process different aversive sensory modalities. Preliminary evidence using chemogenetic inhibition of $Vglut2^+$ LHb neurons suggests that this structure is required for the promotion of itch-evoked passive immobility, but does not appear to function as a brake on itch-evoked active scratching. Collectively, these results establish the LHb's role in promoting a passive behavioral state during acute itch challenge, and support a model in which the LHb mediates the development of depressive symptoms in association with chronic itch disorders.

Poster Session B

Bioengineering

Poster 1B

[Abstract](#)

Quantification of whole-organ renal metabolic rate of oxygen
Presenter: Rajiv Deshpande | Advisor: Dr. Felix W. Wehrli

Poster 2B

[Abstract](#)

High-throughput and ultra-sensitive extracellular vesicle isolation via electroformed inverse-opal nanomaterials
Presenter: Andrew Lin | Advisor: Dr. David Issadore

Poster 3B

[Abstract](#)

Tuning Viscoelastic IPN Properties for Meniscal Regeneration
Presenter: Karen Xu | Advisors: Drs. Jason A. Burdick and Robert L. Mauck

Cell and Molecular Biology

Genetics and Epigenetics

Poster 4B

[Abstract](#)

Determining the microenvironmental contribution to AML chemoresistance
Presenter: Shovik Bandyopadhyay | Advisor: Dr. Kai Tan

Poster 5B

[Abstract](#)

Massively Multiplexed Base Editing for Cellular Therapeutics and Genetic Diagnosis
Presenter: Niklaus Evitt | Advisors: Drs. Rahul M. Kohli and Junwei Shi

Poster 6B

[Abstract](#)

Selection v. Adaptation: driving forces of therapy resistance in melanoma
Presenter: Jess Li | Advisor: Dr. Arjun Raj

Poster 7B

[Abstract](#)

Defining the lineage of thermogenic perivascular adipose tissue.
Presenter: Alexander Sakers | Advisor: Dr. Patrick Seale

Microbiology, Virology and Parasitology

Poster 8B

[Abstract](#)

A recombinant vesicular stomatitis virus vaccine platform protects IFNAR deficient mice from lethal SFTSV challenge
Presenter: Philip Hicks | Advisor: Dr. Paul Bates

Poster 9B

[Abstract](#)

The novel innate immune-antagonistic effects of the multifunctional ectromelia virus C15 protein
Presenter: Elise Peauroi | Advisor: Dr. Laurence C. Eisenlohr

Poster 10B

[Abstract](#)

Mechanisms of PKR activation and evasion during Adenovirus infection
Presenter: Teddy Steinbock | Advisor: Dr. Matthew D. Weitzman

Genomics & Computational Biology

Poster 11B

[Abstract](#)

Analysis of Developmental Arrest and Treatment Resistance in High Risk T-cell Leukemia
Presenter: Jason Xu | Advisor: Dr. Kai Tan

Immunology

Poster 12B

[Abstract](#)

Maternal and postnatal obesity perturb development of the murine gastrointestinal tract and composition of colon-resident intraepithelial lymphocytes
Presenter: Thomas Samuel Barnett Dubensky | Advisor: Dr. Jorge Henao-Mejia

Poster 13B

[Abstract](#)

The effects of obesity on lung macrophage metabolism and function
Presenter: Sam McCright | Advisor: Dr. David Hill

Neuroscience

Poster 14B

[Abstract](#)

The interplay between DNA methylation and Polycomb silencing in mammalian brain development
Presenter: Daniel Connolly | Advisor: Dr. Zhaolan (Joe) Zhou

Poster 15B

Abstract

Characterizing Vulnerable Cell Types in C9orf72-FTD
Presenter: David Dai | Advisor: Dr. Edward B. Lee

Poster 16B

Abstract

Pathogenic LRRK2 hyperactivity disrupts vesicle transport in the neuronal axon
Presenter: Dan Dou | Advisor: Dr. Erika L.F. Holzbaur

Poster 1B | Bioengineering

Quantification of whole-organ renal metabolic rate of oxygen

Rajiv S. Deshpande, Michael C. Langham, Felix W. Wehrli

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Chronic kidney disease is characterized by a progressive loss of kidney function and affects 15% of US adults. Current measures of kidney function detect dysfunction after irreversible damage may have already occurred. This highlights an unmet need for a biomarker that can detect kidney dysfunction earlier. Renal metabolic rate of oxygen (MRO_2) is a suitable metric because it directly represents renal function and has been found to increase by 40-65% during the early stages of diabetic kidney disease.

MRO_2 is calculated with Fick's principle which follows from conservation of mass: C_{RBC} · Hematocrit · BFR · (SaO_2 – SvO_2), where C_{RBC} is a known constant representing the oxygen-carrying capacity of a red blood cell, BFR is blood flow rate in the inflowing arteries normalized by organ mass, SaO_2 is arterial oxygen saturation (assumed to be 98% in healthy subjects), and SvO_2 is venous oxygen saturation in the draining blood vessel. We have developed an MRI-based method that enables noninvasive quantification of MRO_2 by simultaneously measuring blood flow rate and venous oxygen saturation. This MRI pulse sequence interleaves radial phase-contrast before a background-suppressed T_2-prepared echo planar imaging readout for blood flow rate and T_2 fitting, respectively. T_2 is then converted to SvO_2 via a predetermined calibration curve. Background-suppression reduces partial volume effect by suppressing static tissue signal and takes advantage of signal enhancement from inflowing blood with a series of inversion pulses. This MRI-based method measures the key parameters from a single pass in 18 seconds.

The method was tested in two healthy human subjects (M, 25 years; F, 33 years) after informed consent, at 3 Tesla field strength. During data acquisition, the subjects were asked to breath-hold for 18 seconds and imaged at a slice transecting the left renal artery and vein. The SvO_2 values determined in the renal vein were 86±3%, and 90±3% respectively. These values fall within a previously reported range of 82-91%. Blood flow rates were 220±20, and 170±20 mL/min/100g, respectively. Whole-organ renal MRO_2 values were found to be 190±40, and 120±40 μmol O_2/min/100g, respectively.

This preliminary study demonstrates feasibility in renal MRO_2 quantification. Future directions include further method development, testing in more healthy subjects, and application to quantify renal MRO_2 in patients with type 2 diabetes mellitus.

Poster 2B | Bioengineering

High-throughput and ultra-sensitive extracellular vesicle isolation via electroformed inverse-opal nanomaterials

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Extracellular vesicles (EVs) are 30-200 nm membranous vesicles which contain protein and nucleic acid cargoes relating to their cells of origin, and thus have broad potential as biomarkers in clinical diagnostics. However, current conventional and microfluidic EV isolation methods are hampered by their low sensitivity/specificity, low throughput, difficult fabrication, and incompatibility with clinically-relevant sample volumes. In particular, conventional microfluidic approaches for the isolation of EVs have frequently used devices which feature good sensitivity and specificity, but have low throughput and high vulnerability to clogging. Parallelization of such devices enables the preservation of sensitivity and specificity while also enabling higher flow rates and decreased device failure from clogging. In this abstract, we report the development of a simple-to-fabricate nanofluidic device containing millions of immunomagnetic traps within a thin (~30 μm) electroformed lattice. This device massively expands on the potential for parallelization in nanofluidics by leveraging a novel electroformed porous nanostructure to yield higher density of immunomagnetic traps, higher throughput, and reduced non-capturing device volume compared to both our previous work in this area and other microfluidic EV isolation methods. The performance of the FCC device at different flow rates shows its high sensitivity at flow rates up to 75 mL/hr for MNPs with little non-specific off-magnet capture. This device achieves surface-marker-specific isolation of EV subpopulations with higher throughput and equal or improved sensitivity compared to gold-standard methods. In summary, the FCC device potentially offers an inexpensive, high-throughput, and accurate means for ultra-sensitive EV isolation and characterization.

Poster 3B | Bioengineering

Tuning Viscoelastic IPN Properties for Meniscal Regeneration

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Injectable, acellular, and degradable biomaterials have been increasingly explored as therapeutics for tissue repair, due to their ability to fill defects, recruit endogenous cells, and support extracellular matrix deposition. Classically, cell invasion into scaffolds is controlled through scaffold porosity and/or cell-mediated hydrogel degradation; however, recent work has suggested that viscoelasticity plays a role in supporting cell migration. Here, we harness the favorable properties of distinct hydrogels by combining them into an injectable and cell- degradable interpenetrating network (IPN), whose viscoelastic properties can be controlled to support cell invasion in the context of meniscal repair. These networks are injectable due to the guest-host physical crosslinking of hyaluronic acid (HA), with temporal covalent crosslinking based on transglutaminase crosslinking of gelatin. Increasing the physical network concentration (0 to 5 wt%) correlated with increased loss modulus and tan (delta), a measure of the material's energy dissipation (assessed through rheological measure of moduli across various frequencies). Additionally, the gelatin alone control behaved as an elastic network (no change in G' across frequency), whereas addition of the physical network resulted in viscoelastic properties.
Meniscal fibrochondrocyte (MFC) outgrowth was assessed through transferring MFC spheroids (1000 MFC/spheroid) into IPNs. Notably, there was minimal outgrowth into gelatin-only networks and extensive outgrowth into viscoelastic IPN gels. This approach is highly modular to tailor hydrogel properties via design criteria and ongoing work includes assessing critical macroscopic IPN properties such as toughness, adhesion, and degradation. With these varied properties and the use of common biopolymers, the designed hydrogel presents an important approach towards the translation of acellular materials for tissue repair.

Poster 4B | Cell and Molecular Biology - Genetics and Epigenetics

Determining the microenvironmental contribution to AML chemoresistance

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Acute Myeloid Leukemia (AML) is the most fatal hematologic malignancy in adults, largely due to high rates of relapse following chemotherapy. Minimal residual disease (MRD), the persistence of immunophenotypically, morphologically, or genetically defined leukemia cells at a frequency of <5% following frontline chemotherapy, is a poor prognostic factor for AML. MRD cells in acute leukemia have been shown to localize to endosteal bone marrow regions in murine models, where they may utilize microanatomical niches specialized to support long-term quiescent hematopoietic stem cells to become dormant and gain resistance to chemotherapy, which targets dividing cells. However, these niches are ill-defined in human bone marrow, and it remains unclear whether human AML cells actually interact with canonical stem cell niches as a mechanism to evade chemotherapy. We hypothesize that AML MRD cells interact with cells in protective niches within bone marrow by overexpressing stem cell niche retention receptors, which allows them to acquire chemoresistance. We will employ Co-Indexing by Epitopes (CODEX), a recently developed method to visualize dozens of antibody markers on a single-cell level from fixed human tissue, and single cell RNA sequencing to determine whether chemoresistant AML cells indeed hijack endosteal stem cell niches through overexpressed receptors. These receptor/ligand pairs would represent an attractive target for chemosensitization, which may help reduce AML relapse risk. This project is poised to evaluate whether leukemic cells hijack healthy stem cell niches to evade standard-of-care chemotherapy, and this work has the potential to reveal new therapeutic opportunities to better treat this deadly disease.

Poster 5B | Cell and Molecular Biology - Genetics & Epigenetics

Massively Multiplexed Base Editing for Cellular Therapeutics and Genetic Diagnosis

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Genomic "word processing," the conversion of a targeted DNA sequence to a desired alternative, represents a long-standing goal of genome editing. Recently, single targeted C to T and A to G changes have been made possible by CRISPR Cas9 base editors (BEs), fusion proteins comprised of a catalytically compromised Cas9 nuclease linked to a DNA deaminase. However, simultaneous base editing of multiple genomic loci remains challenging. Here, we leverage the intrinsic RNA processing activity of Cas12a to develop multiplexed Cas12a-deaminase base editors. We demonstrate activity of Cas12a base editors with multiple Cas12a variants and deaminases. When combined with Cas12a CRISPR RNA (crRNA) arrays, these constructs show promise for multiplexed base editing. Multiplexed base editing paves the way for complex genomic reprogramming requiring the modification of multiple genes. Therapeutically, multiplexed editing will facilitate streamlined production of more generalized, increased potency cell-based cancer immunotherapies. Diagnostically, multiplexed editing enables CRISPR screens to elucidate pathogenic variants in polygenic diseases. Biotechnologically, multiplexed editing permits screens for elusive drug targets in the setting of genetic dependencies.

Poster 6B | Cell and Molecular Biology - Genetics & Epigenetics

Selection v. Adaptation: driving forces of therapy resistance in melanoma

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Therapeutic resistance in melanoma has hindered the success of the novel targeted therapies that have been incorporated into clinical practice. There have been various efforts to identify the molecular mechanisms driving melanoma resistance, however, most of such efforts had been focused on genetic mechanisms of resistance. Recent studies have shown that non-genetic changes involving transient fluctuations of the activity of various signaling pathways within a genetically homogenous population can also enable certain rare populations of cells to acquire resistance. The ability of melanoma cells to reprogram in response to treatment with targeted therapies presents a question of whether this development of resistance is a process of selection or one of adaptation. Selection describes a process in which the final phenotype is the *same as the initial phenotype*; in the context of resistance, there is an initial population of cells that is as resistant as the final population of cells that emerges as resistant. In a process of adaptation, however, the final resultant phenotype differs from the initial phenotype; cells that emerge as resistance have altered their phenotype in a way that allows them to survive whereas they would have died if they remained in their initial phenotype. Here we use live imaging and DNA barcode lineage tracking to validate the presence of an adaptation response of resistance development, establish a timescale for the phenomenon, and characterize the generalizability of the phenomenon for different perturbations. The phenomena characterized here could provide a new framework for future studies of cancer and for the development of novel therapies to combat the development of resistance in melanoma as well as other malignancies.

Poster 7B | Cell and Molecular Biology - Genetics & Epigenetics

Defining the lineage of thermogenic perivascular adipose tissue.

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Brown adipose tissue can expend large amounts of energy, and therefore increasing its size or activity is a promising therapeutic approach to combat metabolic disease. In humans, major deposits of brown fat cells are found intimately associated with large blood vessels, corresponding to perivascular adipose tissue (PVAT). However, the cellular origins of PVAT are poorly understood. Here, we determine the identity of perivascular adipocyte progenitors in mice and humans. In mice, thoracic PVAT develops from a fibroblastic lineage, consisting of progenitor cells (Pdgfra+, Ly6a+ and Pparg−) and preadipocytes (Pdgfra+, Ly6a+ and Pparg+), which share transcriptional similarity with analogous cell types in white adipose tissue. Interestingly, the aortic adventitia of adult animals contains a population of adipogenic smooth muscle cells (Myh11+, Pdgfra− and Pparg+) that contribute to perivascular adipocyte formation. Similarly, human PVAT contains presumptive fibroblastic and smooth muscle-like adipocyte progenitor cells, as revealed by single-nucleus RNA sequencing. Together, these studies define distinct populations of progenitor cells for thermogenic PVAT, providing a foundation for developing strategies to augment brown fat activity.

Poster 8B | Cell and Molecular Biology – Microbiology, Virology and Parasitology

A recombinant vesicular stomatitis virus vaccine platform protects *IFNAR* deficient mice from lethal SFTSV challenge

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Severe fever with thrombocytopenia syndrome virus (SFTSV, recently reclassified to Dabie bandavirus) and heartland bandavirus (HRTV) are two recently emerged bunyaviruses with case fatality ratios between 4 and 30%. Lymphopenia, thrombocytopenia, diffuse gastrointestinal symptoms, and elevated fever are seen in symptomatic cases. Coagulopathies and multiorgan failure occur in severe cases and are likely responsible for fatal outcomes. Both viruses are transmitted by tick vectors within their endemic distributions. The geographic distribution of one of the primary vectors of SFTSV, *Haemaphysalis longicornis*, has dramatically expanded over the previous decade and now includes Australia, New Zealand, and the United States. It is unclear how the changing vector distributions of these viruses will affect case rates in humans. The threat these viruses pose to human health caused the World Health Organization to consider SFTSV for its 2018 *Blueprint list of priority diseases*. Fatal SFTSV infections have also been documented in primary veterinary care facilities in cats, and one human death may have occurred following a bite from an infected cat. Numerous animal species in endemic regions exhibit seropositivity to these viruses. It is however unclear if other species develop severe disease when infected or if they can function as viral reservoirs. Despite the threat these viruses pose to human and animal health, no vaccines or therapeutics have been approved to combat an outbreak. To address this need, we developed a first generation SFTSV vaccine using recombinant vesicular stomatitis virus technology.

Recombinant vesicular stomatitis viruses (rVSVs) can be engineered to express the glycoproteins of other viruses. These replication-competent particles are attractive vaccine candidates due to their ability to generate robust B and T cell responses against the heterotypic glycoprotein they harbor. We generated a rVSV by replacing the cognate glycoprotein gene with sequences encoding the SFTSV glycoproteins GnGc (rVSV-SFTSV). Infection of *IFNAR*-deficient mice by rVSV-SFTSV was not lethal but caused dose-dependent weight loss that resolved within 6-8 days. rVSV-SFTSV was not neuropathic when inoculated into the brain of C57BL/6 mice. Vaccination of $Ifnar^{-/-}$ mice with a single dose of rVSV-SFTSV induced high neutralizing antibody titers and protected from lethal SFTSV challenge. Lower SFTSV titers were measured in the serum, liver, kidney, and spleen of vaccinated compared to unvaccinated mice. Additionally, a single dose of rVSV-SFTSV protected Ag129 mice from a lethal challenge with mouse-adapted HRTV. In summary, rVSV-SFTSV demonstrated a favorable safety profile in immunocompetent and immunocompromised mouse models and was cross-protective against lethal challenge with SFTSV and HRTV.

Poster 9B | Cell and Molecular Biology – Microbiology, Virology and Parasitology

The novel innate immune-antagonistic effects of the multifunctional ectromelia virus C15 protein

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The success of poxviruses as pathogens depends upon their extensive antagonism of host immune responses by a large arsenal of immunomodulatory proteins. The C15 protein of ectromelia virus (ECTV, the agent of mousepox) is the largest of the ECTV immunomodulatory proteins and is a member of a well-conserved poxviral family previously studied as inhibitors of T cell activation. We have recently determined that C15 also facilitates viral spread in vivo by 3 days post infection, suggesting a second non-adaptive function of C15. Accordingly, we sought to further investigate this new function and identify the cellular target. We found this replication-promoting effect persists in the absence of T cells but is lessened in NK cell-deficient animals, implying the targeting of NK cells. Further investigation of NK cell function both *ex vivo* and *in vitro* shows that C15 selectively antagonizes degranulation of NK cells but not production of antiviral cytokines. Preliminary data suggests that the full impact of C15 *in vivo* is also reliant upon CD8 T cells, even at this early time point. These results prompt further investigation into the mechanism used by C15 to inhibit these cell types and demonstrate the discovery of a novel second function of the protein, which can selectively antagonize both the innate and adaptive murine immune responses.

Poster 10B | Cell and Molecular Biology – Microbiology, Virology and Parasitology

Mechanisms of PKR activation and evasion during Adenovirus infection

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Protein Kinase RNA-activated (PKR) is a key sensor of double-stranded (ds)RNA produced by viruses. Activated PKR halts global protein synthesis to limit viral replication. Many DNA viruses antagonize PKR, leading to the assumption that they produce dsRNA. However, there is little evidence they do so. Human Adenoviruses (AdV) express a non-coding, virus-associated RNA (VA RNA) that inhibits PKR to enhance translation of viral mRNAs. It was therefore proposed that VA RNA outcompetes viral dsRNA binding to PKR. We examined cells infected by AdV using dsRNA-specific antibodies but could not detect dsRNA during infection with either wildtype (WT) or ΔVA viruses. In contrast, we detected nuclear dsRNA during infection with AdV mutants that poorly splice viral mRNAs. This was associated with nuclear relocalization of active PKR and activation of other dsRNA sensors. In contrast, ΔVA infection did not induce PKR relocalization or activate other dsRNA sensors. These observations suggest differences in mechanisms of PKR activation during infection with ΔVA mutant virus compared to splicing-defective AdV mutants. Cellular dsRNA-binding proteins (DRBPs) are known to regulate PKR activation during viral and non-viral stress, and can do so independently of dsRNA. Using siRNA knockdown, we found several DRBPs regulate PKR activation during WT and ΔVA infection. Of the candidate DRBPs examined, NF90 knockdown specifically enhanced late protein expression and decreased PKR activation during ΔVA, but not during splicing-defective AdV infection. These novel findings suggest that VA RNA may play multiple roles in suppressing PKR activation and promoting viral protein synthesis during AdV infection.

Poster 11B | Genomics and Computational Biology

Analysis of Developmental Arrest and Treatment Resistance in High Risk T-cell Leukemia

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Early T-Cell Precursor Acute Lymphoblastic Leukemia (ETP-ALL) is a treatment resistant type of pediatric leukemia whose biology is poorly understood and new therapies are badly needed. There have been a few studies profiling ETP-ALL using bulk and targeted genomics methods, including an ongoing study that will profile the largest cohort of ETP-ALL patients using bulk whole exome and bulk RNA-sequencing. Unfortunately, because bulk genomic technologies collapse each tumor into one cellular state, these studies are under-resolved to observe sub-clonal patterns in ETP-ALL, which are pertinent to understanding its biology.

To synergize with current efforts to use bulk-genomics to characterize ETP-ALL, we performed single cell transcriptomics (scRNA-seq) and single cell chromatin accessibility (scATAC-seq) profiling on 30 ETP-ALL patients: 10 of which responded to induction therapy, 10 of which had high minimal residual disease after induction therapy, and 10 of which responded to initial therapy but relapsed later. As additional comparator groups, we also profiled 10 typical T-ALL patients, and 10 Mixed Phenotype Acute Leukemia (MPAL) patients.

We mapped leukemic cells back to a healthy transcriptomic and epigenetic reference, which we assembled using single cell RNA-seq and single-cell ATAC-seq from healthy pediatric bone marrow and thymus. As expected, leukemic cells from these different subtypes projected to different areas in hematopoietic development. Non-ETP T-ALL patients had the highest proportions of cells projecting to more mature T-cell states, such as $\alpha\beta$ T cells, and MPAL patients had the highest proportions of cells projecting to myeloid progenitor cells (GMPs). Despite these differences, the dominant projected population of ETP-ALL and MPAL were both lymphoid (CLP/LMPP) progenitors.

We then asked if any cell types were enriched in ETP-ALL patients that did not respond to induction therapy. Our preliminary analysis suggests that CLP/LMPP (lymphoid-primed progenitor-like) proportion is increased in non-responders and that this increase is associated with higher residual disease and worse bone marrow morphology after a month of therapy. In addition, our preliminary analysis suggests that CLP/LMPP populations are transcriptomically different between non-responders and responders, with 277 differentially expressed genes (DEGs) having false discovery rate (FDR) < 0.05. In support of these findings, we found that these transcriptomic differences aligned with differential accessibility of chromatin enriched for transcription factor motifs known to regulate hematopoietic differentiation, such as HOXA9, BCL11A/B, and MEF2A/B/C.

Finally, for each sample processed by single cell assays, in collaboration with the Teachey lab at the Children's Hospital of Philadelphia, we have simultaneously generated a patient derived xenograft (PDX) model by injection of primary blasts into immunodeficient (NSG) mice. Initial profiling of PDX models using scRNA-seq shows that blast transcriptomic state is maintained in PDX. We hypothesize that these PDX can serve as valuable models for in-vivo perturbation of targets learned from single cell transcriptomic and chromatin accessibility analysis.

Poster 12B | Immunology

Maternal and postnatal obesity perturb development of the murine gastrointestinal tract and composition of colon-resident intraepithelial lymphocytes

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Pediatric obesity has reached epidemic proportions worldwide, predisposing children to a broad spectrum of chronic illnesses. Despite considerable focus on managing obesity-associated diseases among adults, how nutrition instigates chronic illness from early development onward remains unclear. Clinical data and animal models suggest a role for systemic inflammation, but the salient immune cell populations and their pathological functions are unknown. High-fat diets (HFD) most immediately affect the gastrointestinal tract epithelium, the largest immune cell depot in the body. Intraepithelial lymphocytes (IEL) interact with the intestinal epithelium from development onward to regulate diverse functions including nutrient absorption, tissue growth, and inflammation. Given the sensitivity of IEL development to environmental variables, we hypothesize that HFD perturbs the composition or function of IELs during childhood to potentiate chronic systemic inflammation.

To discover mechanisms driving the early pathophysiology of obesity, we established a mouse model of pediatric obesity wherein IELs are exposed to HFD starting in utero. After feeding dams HFD and weaning their progeny onto the same diet, we dissected intestines from adolescent mice and profiled IEL subsets by flow cytometry. Consistent with possible immune dysregulation induced by HFD, the composition of IEL subsets known to populate the colon during early development were significantly shifted. Colons of HFD mice exhibited profound atrophy relative to age-matched mice fed a control diet, suggestive of underlying inflammation mediated by IELs.

Colonic IELs expressing the $\gamma\delta$ T cell receptor (TCR) were most significantly decreased by HFD, especially those expressing the CD8$\alpha\alpha$ corepressor of TCR signaling. In contrast, IELs expressing the $\alpha\beta$ TCR and stimulatory CD8$\alpha\beta$ coreceptor expanded. CD8$\alpha\alpha$+ $\gamma\delta$ IELs are thought to develop perinatally and recognize colon antigens to regulate growth, whereas CD8$\alpha\beta$+ IELs are induced after birth against foreign antigens to mediate inflammation. scRNA-seq of IELs and qPCR of candidate antigens will highlight TCR specificities and inflammatory pathways that potentially drive the atrophied colon phenotype of HFD mice. Our preliminary data support the hypothesis that dietary perturbations to IEL development instigate the inflammation underlying obesity-associated pathology. Our early-life HFD model positions us to query basic mechanisms of IEL development for translation to prevent progression of pediatric obesity toward systemic illnesses.

Poster 13B | Immunology

The effects of obesity on lung macrophage metabolism and function

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Obesity is a risk factor for the development of asthma, and obesity-associated asthma (OAA) is more severe and more difficult to treat than atopic asthma. Lung macrophages have been implicated in the regulation of OAA immunopathology, however, the mechanisms by which obesity alters lung macrophages are not well understood. As OAA is often refractory to conventional treatments for atopic asthma, an improved understanding of the contribution of lung macrophages to OAA immunopathology will facilitate the development of targeted therapies for this asthma endotype.

To understand the effects of obesity on lung macrophages and determine the contribution of lung macrophages to OAA-like inflammation, we compared the cellular phenotype, transcriptome, and lipidome of lung macrophages from lean and obese mice. Analysis by flow cytometry found that obesity causes expansion of lung interstitial macrophages with increased intracellular lipid and cell-surface expression of the metabolic activation marker CD9. Additionally, obesity increases lung macrophage expression of lipid metabolism genes (e.g., *Plin2, Lpl, Lipa*). Lipidomic analysis revealed increased abundance of specific long chain fatty acids (LCFAs) in macrophages isolated from the obese lung, and *in vitro* studies demonstrated that these LCFAs are sufficient to induce both cellular-metabolic and inflammatory aspects of obesity-associated macrophage activation. Ongoing studies will investigate the molecular mechanisms by which LCFAs and other lipids alter macrophage metabolism and function and will determine the contribution of obesity-associated macrophages to a model of OAA. Taken together, this work raises the possibility that modulating lung macrophage cellular metabolic pathways may represent a novel avenue for the development of therapies for this severe disease.

Poster 14B | Neuroscience

The interplay between DNA methylation and Polycomb silencing in mammalian brain development

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DNA methylation is a central epigenetic mark that classically occurs on cytosine nucleotides in the CG context, where cytosine is followed by a guanine. However, postmitotic neurons in the mammalian brain contain a unique methylome, with large amounts of non-CG cytosine methylation (mCH) accumulating in early postnatal life. This non-canonical methylation mark is written exclusively by the de novo DNA methyltransferase DNMT3A, and removal of *Dnmt3a* from the central nervous system results in broad transcriptional changes and early lethality in mice. Despite the importance of non-CG methylation in neuronal function, the roles of mCH have been difficult to study *in vivo* given the diversity of cell types in the mammalian brain, as mCH patterns differ significantly across neural cell types. Thus, the principles guiding how mCH patterns are established and the effects of mCH on gene expression remain poorly understood. To address this, we genetically ablated *Dnmt3a* specifically from forebrain excitatory neurons and performed cell type-specific nuclear transcriptome profiling. We uncovered many changes in gene expression, with enrichment for genes targeted by the Polycomb repressive complex 2 (PRC2). Through cell type-specific CUT&RUN profiling, we found that the PRC2-associated histone modification H3K27me3 increases exclusively at loci that lose mCG upon loss of DNMT3A, suggesting an interplay between these two repressive epigenetic pathways. In future studies, we seek to understand how DNMT3A is recruited to the neuronal genome in the developing brain and elucidate how mCH influences gene expression in postmitotic neurons.

Poster 15B | Neuroscience

Characterizing Vulnerable Cell Types in C9orf72-FTD

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Our long-term goal is to understand how *C9orf72* mutations cause frontotemporal dementia (C9-FTD) and frontotemporal lobar degeneration (C9-FTLD). C9orf72 is most highly expressed in microglia, and C9orf72 loss of function has been linked to the development of pathologic microglia. In other diseases, pathologic microglia have been shown to secrete glutamate and induce death in excitatory neurons. In addition to the development of pathologic microglia, C9-FTLD is also characterized by the loss of neurons in superficial cortical layers, resulting in the breakdown of neural networks and dementia. However, a major gap in our knowledge is how microglia contribute to neurodegeneration and what neuron subtypes degenerate in C9-FTLD. We hypothesize that in C9-FTLD, pathologic microglia secrete excess glutamate, contributing to the loss of specific excitatory neuronal subtypes and the breakdown of neural networks. Specific Aim #1 will identify the pathologic microglia subtypes that arise and the neuron subtypes that degenerate in C9-FTLD. We will use computational tools to characterize these subtypes and investigate how the loss of specific neuronal populations results in neural network breakdown. Specific Aim #2 will identify where these pathologic microglia and vulnerable neurons are spatially distributed within postmortem tissue and how their reciprocal interactions are changed in disease. We will investigate how gene expression is altered around these microglia and neuron populations to better understand the molecular landscape in which neurodegeneration occurs. Our studies will reveal how C9-FTLD changes microglia and neurons in specific ways, resulting in neural network breakdown and dementia. We will emphasize how pathologic microglia can contribute to neurodegeneration, enabling the development of microglia-targeted therapies for neurodegenerative diseases.

Poster 16B | Neuroscience

Pathogenic LRRK2 hyperactivity disrupts vesicle transport in the neuronal axon

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Parkinson's disease (PD) is the second-most prevalent neurodegenerative disease and the fastest-growing. Current therapies fail to address the underlying neurodegeneration, and development of improved therapeutics is hindered by poor understanding of the pathogenesis. Dysregulation of autophagy, the essential homeostatic pathway by which neurons clear proteins and damaged organelles, has been implicated in PD. Furthermore, altered synaptic transmission is involved in dementia, a debilitating non-motor PD symptom. A leading candidate that ties together autophagy, synaptic transmission, and PD pathogenesis is leucine-rich repeat kinase 2 (*LRRK2*), mutations in which are the most common genetic causes of PD. LRRK2 has recently been shown to phosphorylate a subset of Rab GTPases which mediate intracellular vesicular trafficking, an important discovery in unraveling the mechanisms downstream of LRRK2. Physiologic axonal autophagy is characterized by smooth retrograde transport of autophagic vesicles (AVs), maintaining complex axonal arborization over long neuronal lifespans. In our recent published work, we used live imaging to demonstrate that mutant LRRK2 substantially impairs axonal AV transport. Our findings suggest that hyperactive LRRK2 promotes an unproductive tug-of-war between retrograde and anterograde motors. Interestingly, our preliminary findings suggest that hyperactive mutant LRRK2 also impairs anterograde axonal transport of synaptic vesicle precursors (SVPs). Our current efforts focus on unraveling the mechanism for deficits in SVP transport due to hyperactive LRRK2. In addition, we are investigating whether other PD-associated mutations cause similar deficits, with the goal of elucidating mechanisms by which multiple causes of PD may converge on a LRRK2-dependent pathway to disrupt neuronal autophagy and synaptic homeostasis.

Poster Session List
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Thomas Samuel Barnett Dubensky	12B	Mentor: Dr. Jorge Henao-Mejia *Maternal and postnatal obesity perturb development of the murine gastrointestinal tract and composition of colon-resident intraepithelial lymphocytes*
John Bernabei	1A	Mentor: Dr. Brian Litt *A normative atlas of intracranial EEG activity and connectivity identifies the seizure onset zone in focal epilepsy*
Ryan Boe	5A	Mentor: Dr. Arjun Raj *Uncorrelated allelic expression suggests transcriptional parameters that create a barrier for propagating expression variability*
Ian Cohn	8A	Mentors: Drs. Christopher Hunter & Boris Striepen *A novel system for tracking CD4+ T cell responses to Cryptosporidium reveals a requirement for type 1 conventional dendritic cells.*
Daniel Connolly	14B	Mentor: Dr. Zhaolan (Joe) Zhou *The interplay between DNA methylation and Polycomb silencing in mammalian brain development*
Eli Cornblath	14A	Mentor: Dr. Danielle S. Bassett *Computational modeling of tau pathology spread reveals patterns of regional vulnerability and the impact of a genetic risk factor*
Suna Cranfill	15A	Mentor: Dr. Wenqin Luo *Establishing the role of the lateral habenula in central itch processing*

David Dai   15B   Mentor: Dr. Edward B. Lee
Characterizing Vulnerable Cell Types in C9orf72-FTD

Rajiv Deshpande   1B   Mentor: Dr. Felix W. Wehrli
Quantification of whole-organ renal metabolic rate of oxygen

Dan Dou   16B   Mentor: Dr. Erika L.F. Holzbaur
Pathogenic LRRK2 hyperactivity disrupts vesicle transport in the neuronal axon

Michael Duong   2A   Mentors: Drs. Ilya Nasrallah & David Wolk
Astrocyte Activation Imaging with 11C-Acetate and Amyloid PET in Mild Cognitive Impairment due to Alzheimer Pathology

Niklaus Evitt   5B   Mentors: Drs. Rahul M. Kohli & Junwei Shi
Massively Multiplexed Base Editing for Cellular Therapeutics and Genetic Diagnosis

Philip Hicks   8B   Mentor: Dr. Paul Bates
A recombinant vesicular stomatitis virus vaccine platform protects IFNAR deficient mice from lethal SFTSV challenge

Erin Hollander   4A   Mentor: Dr. Ben Stanger
Pancreatic ductal adenocarcinoma growth suppression through loss of Mgat5-mediated N-linked complex glycosylation

Karun Kiani   6A   Mentor: Dr. Arjun Raj
Changes in chromatin accessibility is not concordant with gene expression changes in MCF-7 cells

Kate Krauss   12A   Mentor: Dr. Laurence Eisenlohr
MHC class II on type II alveolar cells modulates type I interferon responses to pulmonary β-coronavirus infection

Jess Li   6B   Mentor: Dr. Arjun Raj
Selection v. Adaptation: driving forces of therapy resistance in melanoma

Andrew Lin	2B	Mentor: Dr. David Issadore *High-throughput and ultra-sensitive extracellular vesicle isolation via electroformed inverse-opal nanomaterials*
Lev Litichevskiy	11A	Mentors: Drs. Christoph Thaiss & Mingyao Li *Interactions between aging, dietary restriction, and the gut microbiome*
Sam McCright	13B	Mentor: Dr. David Hill *The effects of obesity on lung macrophage metabolism and function*
Clayton Otter	9A	Mentor: Dr. Susan Weiss *Investigating the role of MERS-CoV NS4a, NS4b, and nsp15 in evading dsRNA-induced innate immune pathways*
Daniel Park	7A	Mentor: Dr. Eric F. Joyce *High-throughput Oligopaint screen reveals druggable targets that regulate chromatin looping*
Elise Peauroi	9B	Mentor: Dr. Laurence C Eisenlohr *The novel innate immune-antagonistic effects of the multifunctional ectromelia virus C15 protein*
Alexander Sakers	7B	Mentor: Dr. Patrick Seale *Defining the lineage of thermogenic perivascular adipose tissue.*
Ariel Shepley-McTaggart	10A	Mentor: Dr. Ronald N. Harty *Ubiquitin Ligase SMURF2 Interacts with Filovirus VP40 and Promotes Egress of VP40 VLPs*
Griffin Spychalski	3A	Mentor: Dr. David Issadore *Extracellular vesicle liquid biopsy to improve breast cancer screening accuracy*
Teddy Steinbock	10B	Mentor: Dr. Matthew D. Weitzman *Mechanisms of PKR activation and evasion during Adenovirus infection*
Stacy Thomas	13A	Mentor: Dr. Gregory L. Beatty *A b-Glucan instructs liver macrophages with anti-metastatic activity*

Jason Xu   11B   Mentor: Dr. Kai Tan
                                               Analysis of Developmental Arrest and Treatment
                                               Resistance in High Risk T-cell Leukemia

Karen Xu   3B   Mentor: Dr. Jason A. Burdick
                                               Tuning Viscoelastic IPN Properties for Meniscal
                                               Regener