CONFERENCE PROGRAM

35th MD PhD National Student Conference

SEPTEMBER 24-27, 2020

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Welcome

Welcome to the 35th Annual MD/PhD National Student Conference!

The Annual MD/PhD National Student Conference is a unique assembly that unites MD/PhD students, alumni, and faculty from across the country to explore the intersections of research and medicine, focusing on career opportunities, healthcare policies, and scientific breakthroughs. The conference offers prestigious keynote speakers, student oral and poster sessions, a diverse career panel, and breakout sessions that encompass various topics of interest to MD/PhD students. This is a great conference to meet colleagues and mentors, learn about opportunities available to MD/PhDs, and discuss exciting science.

Due to the COVID-19 pandemic, the conference is fully virtual. We will be using Socio as our virtual event platform. We plan to take advantage of the virtual format to deliver the highest quality conference possible.

Amidst the COVID-19 global health crisis and the fight for racial equality as a country, the leadership demonstrated by members of the MD/PhD community in seeing patients, research, health policy, and presenting the scientific truth to the public is nothing short of heroism. The pandemic has presented us an opportunity to reconsider our roles, particularly in the public health sector. Given the highly relevant mission of this conference to the crisis, we are planning COVID-19/SARS-CoV-2 relevant sessions for the conference. In addition, we have invited a diverse roster of speakers and panelists, including diversity panelists, to share experiences and work on ways we can increase diversity and inclusion within our MD/PhD community and more broadly as a society.

We will like to extend our utmost gratitude to the invited speakers, panelists, session leaders, and all that make this conference as rewarding as it is. Thank you!

Please consult this conference program to find information on our conference speakers, panelists, breakout sessions, student talks, oral presentations, and much more! Please direct any questions to MDPhDConference@ucdenver.edu.

We hope to see you (virtually!) at the conference!

Sincerely,

35th Annual MD/PhD Student Conference Planning Committee

Amelia Burch
Laurel Darragh
Joe Hsieh
Roy Khair
Frances Li
Brian Lloyd
Hei-Yong "Grant" Lo
Lily Nguyen
Humphrey Petersen-Jones
Soraya Shehata
Dr. Paul Jedlicka (Faculty Advisor)

Meet the Team

Amelia Burch

Hi all- my name is Amelia Burch. I'm a 4th year CU MSTP student and this year's keynote liaison.

When I'm not occluding the middle cerebral artery in mice, you'll find me on the ski slopes, hiking a 14er, sipping craft brews, or struggling to catch my breath on Denver's running trails. My favorite things are as follows: mirrored sunglasses, chocolate chip cookies, my husband when he's not annoying, NPR and neuroscience!

If you have any questions during this conference, don't hesitate to email me at amelia.burch@cuanschutz.edu. I hope you all enjoy yourselves and, please, have a DoorDash burrito on us! Nomnomnom

Laurel Darragh

Hi! My name is Laurel Darragh. I studied Human Biology, Health, and Society at Cornell University before joining the MST Program at the University of Colorado Denver. I currently work in Dr. Karam's lab studying the tumor microenvironment of head and neck squamous cell carcinomas.

When it's not a pandemic and I have some free time, I enjoy skiing and backpacking in the beautiful Colorado outdoors with my partner and our pup.

Joseph Hsieh

Hi! My name is Joe Hsieh. My thesis work investigates the epigenetic regulation of fusion-positive Rhabdomyosarcoma, and I am broadly interested in epigenetics and chromatin biology.

Fun fact: I have now cut down my egg intake from 6+ to on average 3 per day. Still eggnostic to my cholesterol levels though! Hopefully my body isn't scrambling to lower my total cholesterol level over 200mg/dL easy.

Roy Khair

My name is Roy Khair (pronounced care), and I serve as one of the technology directors for this year's virtual conference.

When I am not trying different virtual background on zoom-my favorite is Stanley Hudson from The Office working in the background- I like to cook, read, and watch episodes of Avatar: The Last Airbender on Netflix. Feel free to say hi to me, and I am very excited to meet all of you-from a distance :)

Frances Li

Hi! My name is Frances, and I'm a fourth year MSTP student in a virology lab studying arboviruses (specifically alphaviruses) and factors that can influence viremia during an infection. When I'm not in the lab, I enjoy exploring the beautiful scenery of the Front Range, cooking and trying different cuisines, traveling and learning about various cultures and customs, and playing board and video games.

Fun fact: I tried to finish a giant rainbow cotton candy (pictured here), and I toured around Tokyo on a go-kart in a Winnie-the-Pooh costume.

Brian Lloyd

Hi! My name is Brian Lloyd. My thesis project is focused on the localization and function of synaptic adhesion molecules and am broadly interested in molecular neuroscience as it relates to neuropsychiatric disease.

Fun fact: I studied vocal performance for my undergraduate degree and met my wife when she was assigned to me as a collaborative pianist for my freshman year performances.

Hei-Yong Lo

My name is Hei-Yong but I go by my middle name Grant. I'm a fourth year CU MSTP student. Professionally, I investigate what RNAs are around the centrosome and what mechanisms they use to get there! It's not much, but it's honest work.

Outside of lab, I have a fish tank and red cherry shrimp tank that I very much enjoy taking care of. I have friends sponsor individual fish, such as Gatorade the Gourami – the thirst quencher! I also play DnD, you know, all the nerd stuff.

I am always happy to help answer any questions – you can reach me at hei-yong.lo@cuanschutz.edu

Lily Nguyen

Hi! My name is Lily Nguyen. I am your diversity panel liaison and social media guru! All the tweets you've read was posted by yours truly ♡ Follow me in real life @lilynnguyen!

In the lab, I combine functional genetics and cancer biology to study the role of ERVs in ovarian cancer (September is ovarian cancer awareness month!).

Outside of lab, I like to read, hike, and pick up new hobbies that I will inevitably abandon. My favorite things include pineapple cakes, maple bar donuts, bubble tea, K-pop, DnD, and my not-so-shy cat, Shy.

Fun fact: My moral alignment is chaotic good, and I've only read the 5th book (Goblet of Fire) in the Harry Potter series.

Humphrey Peterson-Jones

Hi! My name is Humphrey Peterson-Jones. I moved to Colorado from Michigan in 2017 and I love it here! Scientifically, I am interested in performing behavioral paradigms with patients that have intracranial electrodes to address fundamental questions in systems neuroscience.

In my free time I love to ski, snowshoe, hike mountains, and go camping.

Soraya Shehata

I'm Soraya Shehata, a keynote liaison and career panel lead. I spend my time in lab working to understand pathologic RNAs involved in neurodegenerative diseases.

I can be found frolicking in Boulder's backyard mountains, trying to ID local birds, or curled up in a hammock with a good book!

Feel free to reach out with any questions!
soraya.shehata@cuanschutz.edu

Conference Schedule

VIRTUAL CONFERENCE SCHEDULE

Times listed in Mountain Daylight Time Zone.

Thursday, September 24th

9:30 – 10:00 AM	Opening Remarks
10:00 – 11:00 AM	**Keynote Address + Q&A: Dr. Yvonne Maldonado, MD**
11:00 – 12:00 PM	Student Poster Session 1
12:00 – 1:00 PM	Break
1:00 – 2:00 PM	**Keynote Address + Q&A: Dr. Robert Satcher, MD/PhD**
2:00 – 3:00 PM	Student Poster Session 2
3:00 – 4:00 PM	After Hours: Personalized PSTP Meetings

Friday, September 25th

9:00 – 10:00 AM	Pre-conference: Personalized PSTP Meetings
10:00 – 11:00 AM	**Keynote Address + Q&A: Dr. Akiko Iwasaki, PhD**
11:00 – 12:00 PM	Career Panel Q&A
12:00 – 1:00 PM	Break
1:00 – 2:00 PM	Breakout Sessions Ethical Challenges of Vaccines for COVID-19 Mindfulness & High Performance Interfacing with Industry
2:00 – 3:00 PM	Diversity in the Physician-Scientist Workforce
3:00 – 4:00 PM	Small Group Discussion: Diversity in the Physician-Scientist Workforce

Saturday, September 26th

10:00 – 11:00 AM	**Keynote Address + Q&A: Dr. Brian Kobilka, MD**
11:00 – 12:00 PM	PSTP Panel Q&A
12:00 – 1:00 PM	Break
1:00 – 2:00 PM	Student Oral Presentation 1 Cancer Biology Structural & Computational Biology
2:00 – 3:00 PM	Student Oral Presentation 2 Immunology Molecular & Cellular Biology

Sunday, September 27th

10:00 – 11:00 AM	Student Oral Presentation 3 General Medicine I Microbiology & Infectious Diseases
11:00 – 12:00 PM	Student Oral Presentation 4 General Medicine II Neuroscience
12:00 – 1:00 PM	Break
1:00 – 2:00 PM	**Keynote Address + Q&A: Dr. Dianna Milewicz, MD/PhD**
2:30 – 3:00 PM	Closing Remarks

*Additional 30 minutes for Q&A after each keynote address, if necessary.

Keynote Speakers

Dr. Akiko Iwasaki, PhD

Dr. Akiko Iwasaki, PhD, is an HHMI investigator and Waldemar Von Zedtwitz Professor of Department of Immunobiology, and Department of Molecular Cellular and Developmental Biology at Yale University. She received her PhD. from the University of Toronto, and her postdoctoral training from the NIH. She has received numerous honors and awards, including the Eli Lilly and Company Research Award, BD Biosciences Investigator Award, and Wyeth Lederle Young Investigator Award. Dr. Iwasaki was elected into the National Academy of Sciences in 2018.

Dr. Iwasaki's research focuses on the mechanisms of immune defense against viruses at the mucosal surfaces. Her laboratory is interested in how innate recognition of viral infections lead to the generation of adaptive immunity, and how adaptive immunity mediates protection against subsequent viral challenge. Her achievements include the demonstration of tissue-specific properties of dendritic cells, discovery of a pathway by which immune responses to viruses can be triggered, development of a mammalian model of a vaginal Zika infection, and formulation of the "prime and pull" vaccine strategy.

Dr. Brian K Kobilka, MD

Dr. Brian K Kobilka, MD, is a recipient of the 2012 Nobel Prize in Chemistry along with Robert Lefkowitz for studies of G-protein-coupled receptors. He earned his MD from Yale University School of Medicine, and worked as a postdoctoral fellow under Robert Lefkowtiz at Duke University where he started work on cloning the β2-adrenergic receptor. He is currently a professor in the Department of Molecular and Cellular Physiology at Stanford University. In addition to the Nobel Prize, he has received the ASBMB Earl and Thressa Stadtman Distinguished Scientist Award, John J. Abel Award in Pharmacology, and Javits Neuroscience Investigator Award. Dr. Kobilka was elected into the National Academy of Sciences in 2011.

Dr. Kobilka's research focuses on the structure and activity of G protein-coupled receptors; in particular, his work determined the molecular structure of the β2-adrenergic receptor. He is a founder of the biotech company ConfometRx, developing GPCR-based drug discovery technologies. Currently, Dr. Kobilka's lab is interested in receptor structure, intracellular trafficking of adrenergic receptors, and physiologic relevance of adrenergic receptor subtype diversity.

Dr. Dianna M Milewicz, MD, PhD

Dr. Dianna M Milewicz, MD, PhD, is the President George H.W. Bush Chair of Cardiovascular Medicine, Director of the Division of Medical Genetics and Vice-Chair of the Department of Internal Medicine at the University of Texas Health Science Center at Houston McGovern Medical School. She has received numerous honors and awards, including the Antoine Marfan Award, the Doris Duke Distinguished Clinical Scientist Award, and the University of Texas Presidential Scholars Award for Excellence in Research. She has been inducted into the American Society of Clinical Investigation and the Association of American Physicians. Dr. Milewicz has been the Director of the MD/PhD Program offered jointly between the University of Texas Health Science Center at Houston and MD Anderson Cancer Center institutions for over 10 years and is Chair of the GREAT MD/PhD Section Committee.

Dr. Milewicz's research focuses on the genes that predispose individuals to aortic aneurysms, aortic dissections, and cerebral aneurysms. Her lab identifies pathways leading to these vascular diseases and establishes improved therapeutics and biomarkers.

Dr. Robert L Satcher, MD, PhD

Dr. Robert L Satcher, MD, PhD, is an Associate Professor in the Department of Orthopaedic Oncology at The University of Texas MD Anderson Cancer Center. His work with MD Anderson's Global Oncology enterprise is focused on building relationships with international healthcare partners that will lead to the construction of a Cancer Center in sub-Saharan Africa. Dr. Satcher co-founded the eHealth Research Institute (eHRI) to bring together physicians with academic and industry researchers to improve access to specialized health care using the latest in research and technology.

Dr. Satcher's research focuses on the bi-directional interactions between cancer cells and bone cells that play a critical role in bone metastasis formation. Toward this end, they have established unique interdisciplinary approaches, combining oncology, bioengineering, molecular biological fields, and continue to seek translational partnerships. We have discovered that renal cell bone metastasis evolve distinctly from other bone metastasis from solid tumors. Dr. Satcher is also a former Astronaut, having served as a mission specialist who visited the International Space Station. He has logged more than 259 hours in space, including 12 hours and 19 minutes in two EVAs.

Dr. Yvonne Maldonado, MD

Dr. Yvonne "Bonnie" Maldonado, MD, is Professor and Chief of the Division of Infectious Diseases and Department of Pediatrics at Stanford Medicine. She is the Senior Associate Dean of Faculty Development and Diversity. She directs Stanford's Global Child Health Program and serves as the Medical Director of Infection Prevention and Control. Dr. Maldonado was an Epidemic Intelligence Service Officer at the CDC, and has led several NIH, CDC, WHO, and Gates funded domestic and international pediatric vaccine studies.

Dr. Maldonado's research focuses on epidemiologic aspects of viral vaccine development and prevention of perinatal HIV transmission. Her research includes studies of the impact of rotavirus, measles, and polio vaccines on the epidemiology and prevention of childhood infections in low resource populations. One major project has been to identify and improve the molecular epidemiology of factors affecting the immunogenicity of oral polio vaccine. Currently, her lab is leading efforts to improve diagnostics and understanding of SARS-CoV-2 transmission. Her work on SARS-CoV-2 includes studying the accuracy of different nasal swab techniques, the route and progression of coronavirus transmission within a household, and the efficacy of select antiviral drugs.

Breakout Sessions

Ethical Challenges of Vaccines for COVID-19

A review of ethics pertaining to research, allocation of scarce vaccines, global distribution, and mandates.

Arthur L Caplan, PhD, NYU School of Medicine

Dr. Arthur L Caplan, PhD, is the founding head of the Division of Medical Ethics at NYU School of Medicine. He has served on national and international committees, including chair of the Advisory Committee to the United Nations on Human Cloning.
During the COVID-19 pandemic, Dr. Caplan established a working group on coronavirus vaccine challenge studies, developed an ethical framework for distributing drugs and vaccines for J&J, and is a member of the WHO advisory committee on COVID, Ethics and Experimental Drugs/Vaccines.

Mindfulness and High Performance

What is it? What are the ingredients? What do mindfulness and attention have to do with high performance??

Roberto P Benzo, MD, Mayo Clinic

Dr. Roberto P Benzo, MD, is an esteemed physician-scientist and the founding director of the Mindful Breathing Laboratory at the Mayo Clinic. Dr. Benzo and his research team seek to improve the quality of life for people with life-limiting conditions through interventions such as meditation, behavior change, rehabilitation, and physical activity. His research explores the potential beneficial effects of mindfulness practices and patients' willingness to participate in their own health (participatory medicine) on health outcomes in people with chronic lung disease.

How to Interface with the Biomedical Industry to Translate Preclinical Diagnostics & Therapeutics to the Clinic

Amir Nashat, PhD, Polaris Partners

Dr. Amir Nashat, PhD, is a managing partner at Polaris Venture Partners. He currently serves and has served as director of several biotechnology companies, including AgBiome, Dewpoint Therapeutics, Fate Therapeutics, Selecta Biosciences, Syros Pharma and aTyr Pharma. He focuses on investments in healthcare.
Dr. Nashat's doctoral research focused on information flow through neurons, neural implants and neural tissue engineering. He holds a PhD in chemical engineering from MIT.

Physician-Scientist Training Program (PSTP)

Albert Einstein College of Medicine

Moshe Sadofsky, MD, PhD (Pathology)

Baylor University

Carl Allen, MD, PhD (Pediatrics)

Duke University

Allison McElvaine, PhD (Director)

Emory University

Ann Chahroudi, MD, PhD (Pediatrics)

Harvard University

Jatin Vyas, MD, PhD

Icahn School of Medicine at Mt. Sinai

Maria de las Mercedes Perez-Rodriguez, MD, PhD (Director)

Ohio State University

Robert Baiocchi, MD, PhD (Director)

Stanford University

Joy Wu, MD, PhD (Internal Medicine)

University of California, Los Angeles

Olujimi Ajijola, MD, PhD (Internal Medicine)

University of Iowa

David Stoltz, MD, PhD (Director)

University of Minnesota

Erik Peterson, MD (Associate Director)

University of North Carolina at Chapel Hill

Joseph Duncan, MD, PhD, FIDSA (Director); Simon Gray, MD, PhD; Klara Klein, MD, PhD

Vanderbilt University

Patrick Hu, MD, PhD (Director)

Washington University in St. Louis

Jacqueline Payton, MD, PhD (Clinical Pathology)

Career Panel

Andrew Le, MD

Dr. Andrew Le, MD, is the CEO and Co-Founder of Buoy Health. Started in 2013, Buoy Health operates an artificial intelligence and machine learning-driven health assistant that helps patients self-diagnose and triage to the right care. The start-up company aims to make self-diagnosis and navigating the healthcare system simple and easy.

Dr. Le obtained his MD from Harvard Medical School. He believes in the power of creating technology with heart for the health of every person in the world.

Cheryl Keech, MD, PhD

Dr. Cheryl Keech, MD, PhD, is the Chief Medical Officer and Executive VP of Clinical Research at ILiAD Bio, a company dedicated to the prevention and treatment of diseases caused by *B. pertussis.*

Dr. Keech received her MD from Indiana and PhD in biochemistry and molecular biology from Colorado. She has held senior medical director positions at Eli Lilly and GSK, and was the Global Clinical/Regulatory Director for Access and Delivery at the NGO PATH. She was also the Executive Medical Director at PPD, leading vaccine advancement operations.

Benjamin Young, MD, PhD

Dr. Benjamin Young, MD, PhD, is a CU MSTP alumnus and now is the Senior Global Medical Director at ViiV Healthcare, an organization committed to innovative treatments for the HIV/AIDS community. Dr. Young has lived his career at the intersections of basic science, clinical medicine, public health, and human rights.

Prior to joining ViiV, Dr. Young took on many roles as a physician, scientist, public health expert, and human rights activist. Notably, he was on the WHO HIV Clinical Guideline Development Group. His work resulted in the recommendation of antiretroviral treatment and pre-exposure prophylaxis for all people living with or at substantial risk of HIV. He champions guidelines informed by science and rooted in the principles of health and human rights.

Diversity Panel

Carl G Streed Jr, MD, MPH

Dr. Carl G Streed Jr., MD, MPH, is an Assistant Professor at the Boston University School of Medicine. As a medical student, he advocated for the inclusion of LGBTQ health in the curriculum and worked to achieve transgender equity in health insurance coverage. Nationally, Dr. Streed has chaired the American Medical Association Advisory Committee on LGBTQ Issues and served on the board of GLMA: Health Professionals Advancing LGBTQ Equality. His efforts to improve the health and well-being of sexual and gender minority individuals and communities have earned him many awards, notably from the American Medical Association Foundation, the World Professional Association for Transgender Health, and the Obama White House.

Dr. Streed is the Research Lead for the Center for Transgender Medicine and Surgery at Boston Medical Center. He collaborates with researchers, clinicians, and staff to assess and address the health and well-being of transgender and gender diverse individuals.

Hannah Valantine, MD

Dr. Hannah Valantine, MD, has been appointed NIH's first Chief Officer for Scientific Workforce Diversity since March 2014. Prior to joining the NIH, Dr. Valantine served as Senior Associate Dean for Diversity and Leadership and Professor of Cardiovascular Medicine at Stanford. Her research focuses on the pathogenesis of heart-transplant rejection. Her contributions include the use of echocardiography for evaluating transplant rejection, the role of insulin sensitivity on cardiac allograft outcomes, and the use of cell-free DNA as detection biomarker. In addition to a prestigious career in cardiology, Dr. Valantine is a recipient of the NIH Director's Pathfinder Award for Diversity in the Scientific Workforce.

As NIH's Chief Officer for Scientific Workforce Diversity, Dr. Valantine is diversifying the biomedical research workforce by developing a vision and comprehensive strategy to expand recruitment and retention. Her work promotes inclusiveness and equity throughout biomedical research. Dr. Valantine has spearheaded many initiatives and programs aimed at promoting diversity and fostering mentorship.

John M Carethers, MD

Dr. John M Carethers, MD, is the Professor and Chair of the Department of Internal Medicine at University of Michigan. Dr. Carether's research interests include familial cancer and polyposis syndromes, mechanisms of tumor progression, and colorectal cancer disparities. Dr. Carether's clinical interests are familial colon cancer syndromes, including FAP, HNPCC, Peutz-Jeghers, and colorectal cancer.

Dr. Carethers has a special interest in colorectal cancer disparities as it relates to genetics and outcomes. He was the former PI of the SDSU/UCSD Cancer Center Comprehensive Partnership U54 grant, which addresses cancer disparities. Currently, his lab strives to understand biological differences and approaches to the racial disparity seen in the morbidity and mortality from colorectal cancer. They have demonstrated that African American colorectal cancers possess less frequent microsatellite instability than Caucasians, but possess more frequent EMAST (a poor prognosticator). They also discovered that infiltration of granzyme B immune cells at the invasive tumor borders was markedly lower in African American tumors.

Russell J Ledet, PhD

Dr. Russell J Ledet, PhD, is a third-year medical student in the MD/MBA program at Tulane University School of Medicine and A.B. Freeman School of Business. From 2004 to 2013, he was a cryptologic technician First Class Petty Officer in the US Navy, serving on both active duty and reserve status. Then, he went on to complete a PhD in molecular oncology at NYU utilizing cutting-edge proteomic technology to identify dysregulated protein modifications in treatment-resistant prostate cancer. He is a recipient of multiple awards, including HHMI's Gilliam Fellowship for Advanced Studies.

As President and Co-Founder of medical student-led organization The 15 White Coats, Dr. Ledet plays an active role as an advocate against racial and health disparities. The 15 White Coats affects change by influencing the cultural imagery in K-12 classrooms nationwide, assisting medical school applicants of color to apply to medical school, and creating culturally adept media content. In addition, Dr. Ledet was a panelist at AACR's Racism and Racial Inequalities in Cancer Research special session held in June 2020.

Sonia C Flores, PhD

Dr. Sonia C Flores, PhD, is the Vice Chair for Diversity and Justice in the Department of Medicine and associate Program Director for Diversity of the Pulmonary Fellowship at the University of Colorado. Dr. Flores has had a long and illustrious career studying pulmonary complications of HIV infections.

In her position as the Vice Chair for Diversity and Justice, Dr. Flores has initiated many programs to foster inclusion and equity. She has started foundational bias workshops aimed at exploring and addressing implicit bias from and towards patients, peers, and supervisors. She has implemented a model of peer coaching aimed at decreasing burnout in fellows and postdocs by addressing issues of identity, self-efficacy, and cultural capital. In addition, she leads the Graduate Experiences for Multicultural Students (GEMS) program, which recruits undergraduate and medical students from populations under-represented in science and medicine and provides a summer research experience. The program has already trained more than 270 students interested in biomedical research areas.

Statement of Diversity & Inclusion

The ongoing protests following George Floyd's death in May are bringing light to long-standing and deep-rooted inequalities afflicting our communities. These events have highlighted the fact that racial inequality and a lack of diversity have caused irreversible harm to the Black community, including aspiring and existing members of our very own medical and scientific community. Among MD/PhD applicants and matriculants, the proportion of American Indians or Alaska Natives, Blacks or African Americans, Hispanics or Latinos, Native Hawaiians or Other Pacific Islanders students (URMs as defined by NIH) is grossly underrepresented across the country[1]. As planners of a conference that values inclusivity and diversity, we feel this fact, along with other widespread inequalities in our society, is unacceptable. Now, with the attention and support of medical program directors, congresspeople, and policymakers everywhere, there are opportunities to create meaningful change that is long overdue.

The goal of this conference is to provide a venue for MD/PhD students to better prepare for careers in medicine and science. This includes having open and frank discussions of how to address systemic inequalities. Like diagnosing any disease, recognizing the existing systemic issues is the first step to meaningful, long-lasting growth and change. **As organizers of the 35th Annual MD/PhD National Student Conference, we feel compelled to promote anti-racism, both by implementing changes within our own organization as well as advocating for change at a broader level. This year, we are taking action to increase diversity and end racial inequality, by implementing changes to the conference and advocating for change.**

Each year, we dedicate $10,000 for travel awards for underrepresented minorities or individuals from disadvantaged backgrounds. At this year's conference, we are allocating significantly more resources towards efforts to increase diversity both locally and nationally:

- We actively sought out speakers from disadvantaged background/underrepresented minority.
- We have increased the number of diversity awards for this conference from 10 to 65.
- We will seek opportunities to expand on funds for diversity awards each year.
- We have incorporated a session specifically dedicated to discussing what we, as a community, can do to increase diversity and decrease racial injustice in the sciences and medicine. We hope to have events to address these issues each year.
- We have established smaller, more intimate sessions to brainstorm actionable items to bring back to our home institutions to implement change nationally.
- We are listening and want to hear your suggestions and recommendations about what you would like to see at the conference and how you would like this discussion to go. Whether you have a story you want to share, ideas to brainstorm about enacting tangible change, or feedback on how we could do things better, we would love to hear from you.

We will continue this discussion and provide more details as the conference approaches. Contact us here to share your experiences and thoughts: **MDPhDConference@ucdenver.edu**

1. Akabas and Brass, "The national MD-PhD program outcomes study: Outcomes variation by sex, race, and ethnicity." JCI Insight: insight.jci.org/articles/view/133010

Diversity Award Guidelines

Diversity Award Guidelines

The MD/PhD Student Conference Planning Committee is dedicated to making the event available for all MD/PhD students throughout the country. We believe having a more diverse population at the conference will benefit every student in training. Diversity Awards reimbursing registration costs are being offered. In years past, 10 awards were granted, but given the virtual conference of this year, we have increased the slots to 65.

Diverse students are broadly defined by the NIH as follows:

- **Individuals from racial and ethnic groups that have been shown by the National Science Foundation to be underrepresented in health-related sciences on a national basis.** The following racial and ethnic groups have been shown to be underrepresented in biomedical research: American Indians or Alaska Natives, Blacks or African Americans, Hispanics or Latinos, Native Hawaiians or Other Pacific Islanders.
- **Individuals with disabilities**, who are defined as those with a physical or mental impairment that substantially limits one or more major life activities.
- **Individuals from disadvantaged backgrounds**, including those coming from a social, cultural, or educational environment that has recently, demonstrably and directly inhibited the individual from obtaining the knowledge, skills, and abilities necessary to develop a research career. Such environments may include rural or inner-city settings.

Note: Applications related to disadvantaged backgrounds are difficult to justify for students at the graduate level. Under extraordinary circumstances, the selection committee, at its discretion, may consider applications related to disadvantaged backgrounds. Such decisions will be made on a case-by-case basis and the student must supply supportive explanations and documentation. Additional information about diversity qualification can be found at: https://researchtraining.nih.gov/resources/faq#867

Recipients will be chosen on a competitive basis by a review committee. The key criterion for selection will be the quality of the research abstract submitted by the award applicant describing their recent scientific work. For incoming and 1st year MD/PhD students, abstracts can cover research completed as undergraduates or technicians, whereas more senior MD/PhD students should submit work based on graduate laboratory rotations or thesis work.

To apply, register and submit an abstract by Sept. 1st and select "Consideration for Diversity Award". If selected, a 100% refund on registration cost will be granted. Applicants must complete the following:

1. Register and submit a research abstract. Indicate the diversity category for which you are eligible.
2. If desired, submit an explanation on why you qualify for a diversity award up to 2000 characters long.

Please do not hesitate to let us know if you have other further questions by contacting us at MDPhDConference@ucdenver.edu

Diversity Award Recipients

The following students have been selected, based on the diversity guidelines as defined by the NIH, for this year's Diversity Awards. Congratulations!

Elorm Agra
Alexander Baez
Dene Betz
Briana Christophers
Trong Phat Do
Leanne Dumeny
Safwan Elkhatib
Jacob Elnaggar
Carolina García García
Jasmine Geathers
Alexandra Goetjen
Alicia Ivory
Laura Marquez Loza
Lauren Morehead
Erica Osta
Shakoora Sabree
Jerricho Tipo
Kenneth Valles
Camila Villasante
Jamarius Waller
Anne Wells
Briana Wilson
Jesus Zamora-Pineda

Student Oral Presentations

Cancer Biology

Daniel Kwon, University of British Columbia

Targeting Mantle Cell Lymphoma Using a CXCR4-directed Radiotheranostic

Kwon, D.,Takata, K., Zhang, Z., Chong, L., Fraser, B., Uribe, C., Zeisler, J., Takata, T., Merkens, H., Kuo, H-T., Zhang, C., Lau, J., Lin, K-S., Steidl, C., Benard, F.

Introduction: Mantle cell lymphoma (MCL) is a B-cell non-Hodgkin's lymphoma with poor survival rates; relapsed MCL is especially aggressive and resistant to standard immunochemotherapy. The C-X-C chemokine receptor 4 (CXCR4) is highly expressed in hematological malignancies and has been implicated in the homing of MCL cells to the stroma of the bone marrow, potentially enabling relapse and resistance. We explore CXCR4 as a potential target in MCL for a targeted imaging and therapeutic approach via a novel radiotheranostic, [68Ga]Ga-/[177Lu]Lu-BL02.

Methods: Immunohistochemical (IHC) staining for pCXCR4 was performed on biopsy samples from a cohort of MCL patients (n = 146). MCL (n = 11) and other lymphoma cell lines (n = 26) were assessed for CXCR4 expression by RNA sequencing, flow cytometry and IHC staining. BL02 was synthesized via solid-phase peptide synthesis and radiolabeled with either [68Ga]GaCl3 or [177Lu]LuCl3. PET imaging and biodistribution studies of [68Ga]Ga-BL02 were done on Daudi, GRANTA519, Jeko1, Z138 and PC3 xenograft-bearing NRG male mice. SPECT imaging, biodistribution, and radionuclide therapy studies of [177Lu]Lu-BL02 were performed on Z138-bearing NRG male mice. Statistical analyses were performed using R version 3.4.0.

Results: Positive pCXCR4 expression in MCL patients (n=91) correlated with worse survival (p=0.005) and was a negative independent prognostic factor. CXCR4 expression in MCL cell lines were near-universally elevated and comparable to other lymphoma cell lines. Based on RNA-sequencing and flow cytometry, we performed PET imaging and biodistribution studies at 1 post-injection (p.i.) on Z138 (high), Jeko1 (high) and GRANTA519 (low) MCL xenograft models, alongside Daudi (Burkitt Lymphoma, positive control) and PC3 (prostate adenocarcinoma, negative control) xenografts models. [68Ga]Ga-BL02 to demonstrate high imaging contrast and differential uptake in xenograft models, which was correlated to CXCR4 expression based on IHC and flow cytometry. Biodistribution studies of [177Lu]Lu-BL02 at 1, 4, 24 and 72 h p.i. of Z138 mice showed high and sustained tumor uptake over a period of 72 hours. SPECT imaging using [177Lu]Lu-BL02 of Z138 xenografts correlated with the biodistribution results and showed high radioactivity retention in tumour and low healthy tissue uptake. Radionuclide therapy studies in Z138 xenograft models (500±180 mm3) using [177Lu]Lu-BL02 showed rapid regression of tumor volume in the treated group (28 MBq, n = 8), with an mean tumor volume of 3.0±4.0 mm3 and 75% of mice achieving remission by Day 10. In contrast, tumours in the control group (PBS, n = 8) showed exponential growth and all mice reached the study endpoint by Day 10 (>1500 mm3).

Conclusion: [68Ga]Ga-BL02 and [177Lu]Lu-BL02 represent an effective method of diagnosing and treating CXCR4-expressing malignancies, with the potential to target prognostically-poor MCL.

Carson Wills, Penn State University

Chemotherapy Promotes Breast Cancer Metastasis Through Extracellular Vesicle Secretion

Wills, C., Liu, X., Chen, L., Zhao, Y., Sundstrom, J., Wang, HG.

Introduction and Background: Neoadjuvant chemotherapy (NAC) is the standard of care for patients with locally-advanced breast cancer. However, a subset of patients develop distant metastases following treatment, and evidence suggests that NAC itself may promote metastasis in some patients. Extracellular vesicles (EVs) have recently emerged as important regulators of tumor metastasis through the horizontal transfer of biologically-active material. The purpose of this research is to determine how EVs derived from chemotherapy-treated tumor cells regulate metastasis in order to develop more effective chemotherapeutic options for breast cancer patients.

Specific Experimental Aims: The goals of this project are to determine how chemotherapy regulates the secretion and content of breast tumor-derived EVs in vitro, and to elucidate the mechanism by which these EVs accelerate breast cancer metastasis in vivo.

Methods and Design: EVs were isolated from the conditioned media of human triple-negative breast cancer (TNBC) cells treated with low-dose Doxorubicin (DXR) or vehicle control (DMSO). Bioluminescent imaging was used to quantify primary tumor progression in xenografted mice treated with DXR, EVs, or PBS; as well as whole-body metastasis in mice pre-treated with EVs followed by tumor cell injection.

Results: In a xenograft mouse model of TNBC, we confirm that DXR treatment decreases primary tumor growth while promoting pulmonary metastasis. In models of both highly-and poorly-metastatic TNBC, we demonstrate that sublethal doses of DXR significantly enhance EV secretion in vitro compared to control. Xenografted mice treated with EVs derived from DXR-treated cells (DXR-EVs) demonstrate a significant acceleration in metastasis with no increase in primary tumor growth compared to control EV or PBS treatment. Although DXR-EVs do not enhance tumor cell migration or invasion in vitro, they demonstrate preferential organotropism to the lungs and liver in vivo. Mice pre-treated with DXR-EVs prior to tail vein injection of tumor cells demonstrate a significant increase in metastatic tumor burden compared to mice pre-treated with control EVs or saline. Using proteomic analysis, we identify differentially-expressed EV proteins upregulated by chemotherapy treatment, and utilize CRISPR-Cas9-mediated gene knockout to determine that a glycoprotein upregulated in DXR-EVs is critically involved in EV-mediated metastasis.

Conclusions and Future Directions: This research proposes a novel mechanism of chemotherapy-induced metastasis by which organ-specific uptake of EVs derived from chemotherapy-treated cells primes the pre-metastatic niche, creating a favorable environment for metastatic tumor growth. Future directions include expanding this model to other tumor types, and further elucidating the mechanism by which EVs prime the pre-metastatic niche.

Adam Grippin, University of Florida

Customizable mRNA-nanoparticles for treatment of glioblastoma

Despite aggressive chemotherapy, surgical resection, and radiation therapy, glioblastoma (GBM) remains almost uniformly fatal. Cancer vaccines have shown promise as therapies for GBM but even the most effective vaccines work in only a subset of patients due to failure to initiate antitumor immune responses or failure to overcome the immunosuppressive microenvironment around the brain tumor. Future cancer vaccines should improve survival in a greater proportion of patients and enable early prediction of patient response to treatment.

Nanoparticles with therapeutic and prognostic capability have been proposed to solve each of these problems, but the vast majority of nanoparticle-based products fail to reach clinical utility. The few that have reached clinical use have failed to demonstrate substantial benefit in late-phase clinical trials.

Here, we report development of versatile nanoparticles composed of lipids and mRNA (RNA-NPs) that can be customized to enhance cell-based vaccines or reprogram the brain tumor microenvironment.

First, we demonstrate that RNA-NPs are more effective than standard techniques (i.e. electroporation) at both transfecting and activating dendritic cells. We find that IO-RNA-NPs dramatically change gene expression profiles in DCs compared to electroporation, leading to increased expression of costimulatory markers, production of inflammatory cytokines (e.g. IFN-α), and enhanced migration to lymph nodes. Importantly, we also demonstrate that DCs loaded with RNA encoding tumor antigens via IO-RNA-NPs inhibit tumor growth in a treatment model in which RNA electroporated DCs yield no benefit. Furthermore, loading these nanoparticles with iron oxide enables MRI-based prediction of individual outcome. Substantial reduction in T2*-weighted MRI intensity in treated lymph nodes two days after vaccination correlates strongly with reduced tumor size 2-5 weeks after vaccination and predicts a 100% increase in median survival compared to treated mice without this change. Taken together, our findings demonstrate that these DC-activating IO-RNA-NPs stimulate robust inhibition of tumor growth and enable early prediction of antitumor response to DC vaccines with a widely available imaging modality.

We then demonstrate that simple modifications to particle chemistry can dramatically change localization of systemically injected particles. We report that the addition of cholesterol to the RNA-NP backbone enables uptake in intracranial glioblastoma tumors. This uptake is specifically in the immune compartment of these tumors, with a preference for tumor associated macrophages. We demonstrate that these particles not only increase expression of reprogram these cells into immune activating phenotypes (e.g. increased MHC II and CD80 expression), but also can be used to deliver immune modulatory nucleic acids to these cells. We demonstrate that loading these nanoparticles with siRNA encoding PD-L1 enables suppression of PD-L1 expression, leading to significantly improved survival response to systemic checkpoint blockade in mice with intracranial gliomas.

Overall, we demonstrate that RNA-NPs are a versatile platform for RNA delivery to immune cells. These particles are currently under investigation in canine trials with human clinical trials planned for this year.

Structural & Computational Biology

Evan Waldron, Rutgers University

The Structural Basis of DSF Signaling

Waldron, E.J., Snyder, D., Fernandez, N.L., Sileo, E., Inoyama, D., Freundlich, J.S., Waters, C.M., Cooper, V.S., Neiditch, M.B.

Introduction and Background

The diffusible signal factors (DSFs) are a family of fatty acids that are produced and detected by numerous Gram-negative bacteria as quorum-sensing autoinducers (AIs). DSFs are produced by the synthase RpfF to contain a signature cis-2 double bond critical for their detection by the DSF receptor RpfR. In multiple human pathogens, DSFs regulate diverse phenotypes, including virulence factor expression, antibiotic resistance, and biofilm dispersal through the bacterial second messenger cyclic-di-GMP. Despite their widespread relevance to human health, the molecular basis of DSF recognition by their cellular receptors remained a mystery. We report the first structure–function studies of the DSF receptor RpfR and its interaction with the DSF synthase RpfF.

Specific Experimental Aims

Describe the molecular basis of DSF recognition and the importance of the cis-2 double bond to DSF function.

Investigate the molecular basis for the DSF synthase-receptor interaction between RpfR and RpfF.

Methods and Design

All structures were determined using X-ray crystallography. Structurally guided mutants designed to disrupt DSF binding and the RpfR-RpfF interaction were generated in Burkholderia cenocepacia. BDSF and c-di-GMP levels as well as biofilm fitness of mutants were compared to WT strains. RpfF activity in the presence and absence of RpfR (FI) was measured in vitro.

Results

We present the X-ray crystal structure of the RpfR DSF-binding domain in complex with the Burkholderia DSF (BDSF) and additionally the structure of the DSF-binding domain in complex with the inactive, saturated isomer of BDSF, dodecanoic acid. We further report the discovery of a previously overlooked RpfR domain and show that it binds to and negatively regulates the DSF synthase RpfF. We have named this RpfR region the RpfF interaction (FI) domain, and report its structure alone and in complex with RpfF. Throughout cellular growth, BDSF production by RpfF is post-translationally controlled by the RpfR FI domain, affecting the cellular concentration of the bacterial second messenger c-di-GMP.

Conclusions and Future Directions

We described the molecular basis for the binding and specificity of a DSF for its receptor and reported a newly discovered receptor–synthase interaction regulating bacterial AI production and second messenger signal transduction. Future work will investigate if the RpfR-RpfF interaction allows DSFs to regulate their synthesis via negative feedback.

Kumar Thurimella, Cambridge University / University of Colorado

Employing Metabolomics and Microbiome Data to Build Algorithms for Interrogating Host-Microbe Interactions

Thurimella, K., Shaffer, M., Lozupone, C.

Introduction and Background:

The microbiome has been linked to the pathogenesis and salubrious states in the human body. However, recent research has been driven by correlative studies, linking an unfavorable disease state to certain microbes. Untargeted metabolomics approaches have yielded an abundance of datasets but the complexity of the data interpretation remains. We introduce AMON: Annotation of Metabolite Origins via Networks and SCNIC: Sparse Cooccurence Network Investigation for Compositional data as tools to help address these issues. Both are open source software tools used to label compound origins of certain metabolites, from microbe to host or both, to then build a higher level groups of microbes that co-exist together.

Specific Experimental Aims:

Through the integration of these software tools, we hope to be able to use dimensionality reduction while still preserving inherent microbial biology. We hope to group certain metabolites and microbes, while still maintaining phylogenetic truth. With the metabolite origin data, we can thus describe how microbes may interact with each other through different compounds.

Methods and Design:

We illustrate the utility of AMON and SCNIC using a dataset (16s rRNA) from the gut microbiome and blood metabolome (LC/MS) of HIV positive individuals. This validation was part of a larger study of differences in fecal microbiomes in HIV and non-HIV populations. AMON uses KEGG Orthology to generate pathway enrichment and a hypergeometric test to verify the prediction of metabolites and their origin. SCNIC uses a microbiome table to build a correlation network and groups of microbes are clustered together and collapsed into a smaller microbiome table.

Results:

After benchmarking SCNIC, the optimal parameter values were an R-value above 0.5 for the SMD algorithm and for a gamma value above 0.1 for the LMM algorithm. With AMON applied to the data, 40 compounds were produced by bacteria alone, 58 by the host alone and 91 by both. Together, these analyses show that AMON can be used to predict the putative origin of compounds detected in a complex metabolome and SCNIC can help understand microbial dynamics.

Conclusions and Future Directions:

The limitations of integrating metabolomics and metagenomics are stark for complex microbial communities, where there are fewer genes of known function. With these tools, researchers can build a general framework to understand the specific interactions between certain microbes and the host, at a chemical level. Ultimately the understanding of microbiome interactions can influence many aspects of human health and disease through its metabolic activities, and with an understanding we can begin to develop more targeted therapies to mitigate human disease.

Alex Casella, University of Maryland

Characterizing enhancer-driven transcriptional networks in schizophrenia.

Casella A.M., Funk C.C., Price N.D., Colantuoni C, and Ament S.A.

Introduction and Background

More than 90% of genetic risk loci for complex traits are located in non-coding regions of the genome, suggesting that perturbations in regulatory regions may be involved in the development of these traits. It is thought that disruption of transcription factor (TF) binding sites in enhancer regions may be a mechanism by which risk variants affect these phenotypes, but we lack adequate tools to connect these disruptions to genetic risk. Here, we developed a method, the Regulome Wide Association Study (RWAS), to test for associations of binding sites for specific TFs with genetic risk for disease.

Specific Experimental Aims

1) Create an extensible computational tool that connects genetic risk with enhancer characteristics.

2) Use this tool to identify neurodevelopmental TF-target networks that may be disrupted in schizophrenia.

Methods and Design

Predicted binding sites for 842 TFs were derived from a new database of DNase I footprints in 27 human tissues, and the density of footprints was calculated within known tissue-specific enhancer regions. Next, we calculated genetic associations within each enhancer using summary statistics from large genome-wide association studies (GWAS), and then tested for the over-representation of predicted binding sites for each TF in the enhancers associated with a trait of interest. To demonstrate our approach, we applied RWAS to identify TFs whose predicted binding sites in the human brain were overrepresented in enhancers associated with genetic risk for schizophrenia (SCZ) and other neuropsychiatric traits.

Results

We identified several TFs whose binding sites were associated with risk for schizophrenia, including MEF2C and members of the POU family. We validated our model by studying the associations of the genomic loci containing the genes that encode these TFs with risk for SCZ, as well as disease-associated changes in the chromatin accessibility of each TF's binding sites in post-mortem prefrontal cortex from SCZ cases vs. controls.

Conclusions and Future Directions

Notably, several of the TFs identified in our model are known to be master regulators of neuronal development and have been linked to SCZ in previous studies. This list also includes brain-expressed TFs that have not previously been linked to SCZ, yielding interesting opportunities for follow-up. Thus, we have developed a generalizable approach that integrates GWAS summary statistics with footprint-derived regulatory networks in order to identify transcription factor target networks associated with disease risk.

Immunology

Amanda Ward, University of Virginia

HIV-Cell Membrane Fusion Intermediates are Restricted by Serinc3 and Serinc5

Ward, A.E., Kiessling, V., Pornillos, O., White, J.M., Ganser-Pornillos, B.K., Lukas K. Tamm

Introduction and Background: Serinc3 and Serinc5 are recently described host restriction factors that can block HIV infection by incorporating into budding viral particles and decreasing their ability to infect subsequent cells. Serincs are thought to block the very earliest stages of infection, membrane fusion and cell entry, by an incompletely understood mechanism.

Specific Experimental Aims: Elucidate the mechanism of Serinc3/5's restriction of HIV.

Methods and Design: We used giant plasma membrane vesicles (blebs) as target membranes to study "wildtype" and Serinc-disrupted HIV membrane fusion at a single-particle level by fluorescence microscopy and cryo-Electron Tomography (cryoET).

Results: Using fluorescent reporters of membrane and content mixing, we observed that Serinc3 and Serinc5 cause a minimal defect in the ability of HIV pseudoviruses to bind their receptor, no defect in mixing of the outer lipid leaflets (hemifusion), but a pronounced defect in fusion pore opening. Additionally, cryo-ET of HIV pseudoviruses mixed with blebs showed rearrangements of viral and target membranes and proteins at multiple intermediates of HIV membrane fusion. We found that Serinc3 and Serinc5 increased the number of hemifusion and early fusion product events observed in these tomograms and many of the fusion products have a narrowed neck between former virus and bleb.

Conclusions and Future Directions: These results suggest that Serinc3 and Serinc5 restrict HIV membrane fusion, not by inhibiting a particular intermediate step, but by causing broad changes to the energetics of fusion that enables observation of multiple transient intermediate states. An understanding of how Serincs disrupt HIV membrane fusion will clarify the requirements for normal HIV membrane fusion and identify new viral weaknesses that could become drug targets.

Patrick O'Connell, Michigan State University

SLAMF7 signaling reprograms T cells towards exhaustion in the tumor microenvironment

Patrick O'Connell, Sean Hyslop, Maja K. Blake, Sarah Godbehere, Andrea Amalfitano, Yasser A. Aldhamen

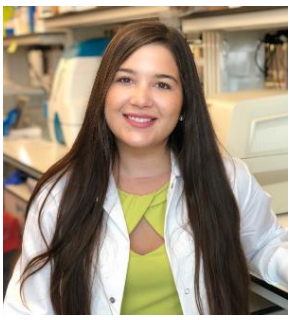
Introduction and background: T cell exhaustion represents one of the most pervasive strategies tumors employ to circumvent the immune system. While tonic T cell receptor signaling is recognized as the primary driving force behind this phenomenon, it remains unknown what other forces drive T cell exhaustion in the tumor microenvironment (TME).

Specific experimental aims/ methods and design: Using both human and mouse systems, as well as, in vitro models, in vivo models, and previously published datasets, we comprehensively examined if the SLAMF7 immune cell receptor plays a role in T cell exhaustion.

Results: Here, we show that the self-ligand SLAMF7 immune receptor is highly co-expressed with multiple inhibitory receptors on human and murine T cells. Activation of SLAMF7 on T cells induced STAT1 and STAT3 phosphorylation, expression of multiple inhibitory receptors (PD-1, LAG3, Tim3), and transcription factors associated with T cell exhaustion (Blimp1, YY1, EZH2). Analysis of The Cancer Genome Atlas revealed that SLAMF7 transcript levels were strongly correlated with various inhibitory receptors, and that high SLAMF7 expression was indicative of poor survival in clear cell renal cell carcinoma (ccRCC). Targeted reanalysis of a CyTOF dataset which profiled the TME in 73 ccRCC patients, revealed cell-type specific SLAMF7 expression patterns, strong correlations between exhausted T cells and SLAMF7+ tumor-associated macrophages (TAMs), and a unique subset of SLAMF7highCD38high TAMs. These SLAMF7highCD38high TAMs showed the strongest correlations with exhausted T cells and were an independent prognostic factor in ccRCC. In vivo, B16-F10 tumors showed restricted growth in SLAMF7-/- mice. Analysis of intra-tumoral T cells from these tumors showed high co-expression of SLAMF7 with multiple inhibitory receptors, decreased inhibitory receptor expression, and decreased expression of the T cell exhaustion promoting transcription factor TOX in SLAMF7-/- CD8+ T cells. Additionally, we found that loss of SLAMF7 on CD8+ T cells impaired their ability to progress through the T cell exhaustion developmental trajectory, resulting in fewer terminally exhausted and more intermediately exhausted T cells. Confirmatory ex vivo co-culture studies validated that SLAMF7-SLAMF7 interactions between murine TAMs and CD8+ T cells induces expression of multiple inhibitory receptors.

Conclusions and future directions: These findings identify SLAMF7 as a novel regulator of T cell phenotype and function in the TME.

Carolina Garcia Garcia, UT Houston



Stromal HIF2 regulates macrophage recruitment and polarization in pancreatic cancer

Garcia Garcia, C.J., Huang, Y., Lin, D., Nguyen, N.D., Fujimoto, T.N., Zhao, J., Lee, J.J, Yu, M., Delahoussaye, A.M., Phan, J.L., Maitra, A., Taniguchi, C.M.

Introduction and Background:

Pancreatic ductal adenocarcinoma (PDAC) has a dense, hypoxic, and immunosuppressive stroma that contributes to therapeutic resistance, particularly immunotherapy resistance. One of the major components and producers of stroma are αSMA+ cancer-associated fibroblasts (CAFs).

Specific Experimental Aims:

In this work we aimed to elucidate the function of the hypoxia-inducible factors (HIFs) within the tumor microenvironment.

Methods and Design:

We used a dual recombinase mouse model containing Hif1α lox/lox or Hif2α lox/lox and αSMACreERT2/+; Pdx1-Flp; FSF-KrasG12D/+; Trp53 frt/frt to constrain the deletion of HIFs to αSMA+ CAFs within spontaneous PDACs. Histopathological analyses, bulk RNA-Seq, and scRNA-Seq (23,622 single cells) were performed on tumor samples to better understand the effects of abrogating stromal HIF2. PT2399, a HIF2 inhibitor, was used to treat isolated CAFs and murine macrophage cell lines cultured under hypoxic conditions. We used heterotopic flank and orthotopic PDAC models to test whether PT2399 enhanced response to immune checkpoint blockade.

Results:

CAF-specific loss of Hif2, but not Hif1, suppressed primary tumor growth and improved survival by 50% ($P = 0.0003$). Gene set enrichment analysis revealed a significant correlation between stromal HIF2 knockout and suppression of tumor macrophage recruitment, differentiation, and activation pathways. The conditioned media of hypoxic CAFs treated with PT2399 failed to induce macrophage migration, as compared to that of CAFs treated with vehicle. Moreover, inhibition of HIF2 in CAFs impaired their ability to induce macrophage M2 polarization. Interestingly, deletion of HIF2 in CAFs resulted in a significant reduction of intratumoral immunosuppressive Treg cells. Lastly, PT2399 improved tumor responses to immune checkpoint blockade in two in vivo PDAC models.

Conclusions and Future Directions:

Here we found that loss of HIF2 signaling in CAFs slows PDAC growth and decreases tumor immunosuppression. HIF2 signaling in CAFs regulates the recruitment of immunosuppressive M2 macrophages and its abrogation also results in decreased intratumoral Treg cells. Further understanding of the role of HIF2 in mediating CAFs–immune cells crosstalk could lead to the development of novel therapeutic regimens for PDAC.

Molecular & Cellular Biology

Jamie Courtland, Duke University

Unraveling the Role of the WASH Complex in Neurologic Dysfunction

Courtland, J.L., Bradshaw, T.W.A., Waitt, G., Soderblom, E.J., Ho, T., Rajab, A., Vancini, R., Kim, I.H., and Soderling, S.H.

Introduction: Emerging evidence suggests that mediators of protein trafficking may be critical to cognitive and motor disorders. Neuronal projections are particularly vulnerable to disrupted trafficking because they require protein delivery to their distal processes, which measure tens to hundreds of centimeters in length. The endosome-associated WASH complex has been implicated in protein trafficking in non-neuronal cells by facilitating the formation and scission of cargo-laden vesicles for transport, but its trafficking effects have not been explored within the nervous system. Human mutations in WASH complex components and associated interactors, result in movement and cognitive disorders such as Parkinson's disease, hereditary spastic paraplegia, and intellectual disability, suggesting that WASH complex dysfunction could be causative in the development of these disorders. However, how these mutations manifest in neurologic dysfunction remains unknown.

Objectives: We aim to understand how a human WASH mutation disrupts protein interactions and trafficking at a cellular level, and determine how these effects manifest in neuropathology.

Methods: We generate a mouse model of a human WASHC4 mutation, and utilize spatial proteomics and systems-level analyses to determine the protein network changes caused by WASH disruption. We confirm these alterations in vitro and in vivo using primary neuronal cultures, immunohistochemistry, biochemistry, and transmission electron microscopy. We study the functional consequences of these changes using mouse behavioral assays and human clinical findings.

Results: We first identify the neuronal WASH complex proteome using in vivo BioID, revealing a network of neuronal endosomal proteins it associates with in vivo. Then, to uncover how dysfunction of endosomal WASH leads to disease, we generate a mouse model of a human WASH complex mutation. Using a spatial proteomics approach coupled with a systems-level analysis of protein covariation networks, we find that this mutation destabilizes the WASH complex and significantly perturbs endosomal and lysosomal pathways in mouse brain. Cellular and histological assays confirm that this mutation has a significant impact on neuronal endo-lysosomal trafficking in vitro and in vivo, with evidence of neurodegenerative pathology. Behavioral analyses reveal that disruption of the WASH complex not only impacts cognition, but also causes significant, progressive motor deficits in mice. Remarkably, a retrospective analysis of patients harboring this mutation confirms motor deficits in humans.

Conclusions: Taken together, this work is the first to examine how the WASH complex functions within neurons in vivo. Our results also establish that impaired WASH complex-dependent trafficking drives pathophysiology relevant to movement disorders in humans.

Brad Eckelmann, Texas A&M University

XRCC1 Promotes Replication Restart, Nascent Fork Degradation, and Mutagenic DNA Repair in BRCA2-deficient Cells

Eckelmann B., Bacolla A., Hegde M.L., Tainer J.A., Mitra S.

Introduction/Background: Mutations can confer selective growth advantages on cancer cells, leading to their clonal selection and expansion. Analysis of tumor genome sequences led to the identification of several different patterns of mutations or mutational signatures. Specific defects in DNA repair mechanisms generate unique mutational signatures, linking DNA repair abnormalities to mutation accumulation and genomic instability in cancer cells. Homologous recombination/end joining (HR/HEJ)- deficient cancers with BRCA mutations utilize alternative DNA double-strand break repair pathways, particularly alternative non-homologous end joining or microhomology-mediated end joining (altEJ/MMEJ) during S and G2 cell cycle phases. Depletion of alt-EJ factors, including XRCC1, PARP1 and POLQ, is synthetically lethal with BRCA2 deficiency; yet, XRCC1 roles in HR-deficient cancers and replication stress are enigmatic. Exploration of XRCC1 repair activity in BRCA1/2-deficient cells has significant implications for development of novel chemotherapeutic strategies and understanding of existing strategies targeting POLQ and PARP1.

Specific Experimental Aims: Does replication stress activate altEJ/MMEJ? Does XRCC1 participate in replication stress-activated altEJ/MMEJ? Do BRCA1 and/or BRCA2 suppress replication stress-activated altEJ/MMEJ? Does XRCC1 participate in replication fork dynamics? How does XRCC1's role in replication fork dynamics change in the absence of BRCA2?

Methods and Design: We utilized standard cell culture methods, cell survival (colony survival and MTT) assays, protein-protein interaction assays (co-immunoprecipitation, immunostaining, proximity ligation assay), and DNA damage assays (neutral/alkaline comet assay, foci formation). DNA replication analysis involved DNA fiber staining. DNA repair assays included basic nick ligation assays, linearized plasmid repair in cell and in vitro, and use of a chromosomally integrated DNA repair fluorescence reporter assay. Mutational signature data and TCGA expression data were used to create survival curves.

Results: XRCC1 has a minor impact on cell survival and DNA double-strand break (DSB) repair after replication stress in HR-proficient cells, however it is recruited to sites of replication stress, where it co-localizes with DNA damage response factors. This complex, when isolated, is able to perform altEJ/MMEJ in vitro, and replication stress stimulates altEJ/MMEJ activity. BRCA2 and XRCC1 co-depleted cells are more sensitive to replication stress than cells depleted of one factor alone, and they do not repair DSBs efficiently. Formation and activity of the XRCC1 altEJ/MMEJ repair complex is suppressed by BRCA2. XRCC1 participates in replication fork restart in HR-proficient cells, and moreso in BRCA2-deficient cells. XRCC1 also participates in replication fork degradation and chromosome aberration formation specifically in BRCA2-deficient cells. Finally, XRCC1 and MRE11 deficiency are more strongly correlated with survival in BRCA-deficient breast cancers than BRCA-proficient breast cancers in TCGA.

Conclusions and Future Directions: We identify a novel role for an altEJ/MMEJ-competent protein complex that is enhanced by replication stress at stalled replication forks in BRCA2-deficient cells. XRCC1 and MRE11 promote degradation of forks in BRCA2-deficient cells, presumably exposing microhomologies that are utilized to prime replication restart. Thus, in HR-deficient tumors, resection and annealing mediated by the MMEJ complex may be important for replication fork restart and cell survival. These findings may be relevant to therapeutic strategies targeting POLQ and PARP activities.

Allen Zhu, University of Chicago

Erasing the m6A Eraser to Treat Cancer? A Study of the RNA Demethylase ALKBH5 in Acute Myeloid Leukemia Development

Zhu AC, Shen C, Sheng Y, Robinson S, Jiang X, Dong L, Chen H, Su R, Yin Z, Li W, Deng X, Chen Y, Hu YC, Weng H, Huang H, Prince E, Cogle CR, Sun M, Zheng B, Chen CW, Marcucci G, He C, Qian Z, Chen J

1. Introduction and Background

Acute myeloid leukemia (AML) is a fatal hematopoietic malignancy, characterized by clonal expansion and blocked differentiation of myeloid progenitor cells. Over 70% of AML patients do not survive more than 5 years, so more effective treatments are needed.

N6-methyladenosine (m6A) is the most abundant post-transcriptional internal modification in mRNA. Through its effects on RNA stability, splicing, and translation, m6A influences many biological processes, including embryonic development and cancer, so it must be precisely regulated.

m6A is "written" onto mRNA by METTL3 and is de-methylated by "erasers" ALKBH5 and FTO. We sought to determine whether ALKBH5 plays a role in AML, as it has been found to affect cancer stem cell self-renewal.

2. Specific Experimental Aims

(i) We first sought to determine whether ALKBH5 expression correlates with AML and its prognosis.
(ii) Then we studied the role of ALKBH5 in AML growth, development, and maintenance. Next, we aimed to study the role of ALKBH5 in leukemic stem/initiating cell (LSC/LIC) self-renewal.
(iii) Finally, we identified potential mRNA targets of ALKBH5 in AML.

3. Methods and Design

(i) We used TCGA and TARGET AML patient cohorts to analyze ALKBH5 expression.
(ii) Gain- and loss-of-function studies were done with ALKBH5 shRNA or stable overexpression (OE) in MONOMAC6 or NOMO1 AML cells, and inducible knockdown or KO cells (iCas9) in MOLM13 cells. We also Alkbh5 KO mouse models, and harvested bone marrow to perform colony formation assays.
(iii) RNA-seq, RIP-seq and m6A-seq were used to identify ALKBH5 targets.

4. Results

(i) AML patient cohort analysis showed that ALKBH5 copy number loss is low, and that ALKBH5 is expressed at a higher level in AML compared to normal HPSCs.
(ii) ALKBH5 KD/KO led to inhibition of human AML cell growth, and increase in apoptosis and global m6A. ALKBH5 OE conversely promoted growth. KO of ALKBH5 inhibited MLL-AF9-mediated cell immortalization, and delayed onset of leukemia in mouse bone marrow transplants.
(iii) ALKBH5 KD upregulated many apoptosis and p53 pathways. RIP and m6A-seq, showed that TACC3 was associated with enrichment in ALKBH5. We then showed that TACC3 regulates P21 and MYC levels.

5. Conclusions and Future Directions

We show that ALKBH5 plays critical roles in AML transformation, development and maintenance, and leukemic stem cell self-renewal in an m6A-dependent manner. We also identify a previously unrecognized ALKBH5/m6A/TACC3/MYC signaling axis involved in AML pathogenesis. Targeting ALKBH5 and TACC3 may be a promising therapeutic strategy for AML patient treatment in the near future.

General Medicine I

Ruthellen Anderson, University of South Dakota Sanford

Bending membranes: Sterols lower energetic barriers for curvature generation during clathrin mediated endocytosis

Anderson, R.H., Sochacki, K.A., Vuppula, H., Scott, B.L., Bailey, E.M., Schultz, M.M., Kerkvliet, K.G., Taraska, J.W., Hoppe, A.D., Francis, K.

Introduction and Background

Human disorders of cholesterol synthesis, characterized by the substitution of cellular cholesterol for sterol intermediates, constitute a group of malformation syndromes that broadly affect tissue development and function. Smith-Lemli-Opitz syndrome (SLOS) is perhaps the best described of these malformation syndromes, exhibiting profound neurologic deficits. Acute depletion of cholesterol disrupts clathrin-mediated endocytosis (CME), a fundamental cellular process critical for neurodevelopment and neurotransmission. We hypothesize that structural alteration of plasma membrane architecture by cholesterol depletion and/or precursor accumulation disrupts clathrin-mediated endocytosis, detrimentally affecting neural function within SLOS.

Specific Experimental Aims

We aim to provide mechanistic insight into the role of sterol homeostasis in regulating clathrin-mediated cellular trafficking, explore structure-activity requirements of sterols necessary for supporting CME, and evaluate the functional consequences of altered CME activity within disorders of cholesterol synthesis.

Methods and Design

Altered sterol homeostasis was modeled through small molecule inhibition of the post-squalene cholesterol synthetic pathway as well as fibroblasts, induced pluripotent stem cells (iPSCs), and iPSC-derived neurons derived from subjects with Smith-Lemli-Opitz syndrome. CRISPR/Cas9 gene editing was utilized to fluorescently monitor endogenous CME dynamics in real-time. Vesicular curvature generation in relation to CME assembly was observed through polarized total internal reflection fluorescence (polTIRFM) and platinum replica transmission electron (TEM) microscopy.

Results

We report that disruption of cholesterol synthesis results in striking immobilization of CME and impaired transferrin uptake. Imaging of membrane bending dynamics and CME pit ultrastructure revealed prolonged clathrin pit lifetimes and accumulation of shallow clathrin-coated structures commensurate with total sterol abundance, suggesting progressive impairment of initial curvature generation and formation of the endocytic neck. Furthermore, clathrin trafficking appears robust to sterol identity and total sterol levels correlate with CME productivity. Analysis of Smith-Lemli-Opitz patient fibroblasts and SLOS hiPSC models displayed functional CME deficits.

Conclusions and Future Directions

We conclude that sterols are a biophysical requirement for efficient endocytic trafficking, acting to lower the energetic costs of membrane bending during pit formation and vesicular scission within CME. These findings also suggest loss of CME activity may contribute to cellular phenotypes observed within SLOS.

Joe Mouawad, Medical University of South Carolina

Induction of fibrosis in lung tissues and fibroblasts results in decreased free anti-fibrotic proteins with a corresponding increased packaging in extracellular vesicles.

Joe E Mouawad, Carol Feghali-Bostwick

Fibrosis is characterized by the excessive accumulation of connective tissue components which form the extracellular matrix (ECM). Pulmonary involvement in fibrotic diseases, like Idiopathic Pulmonary Fibrosis (IPF) and Systemic Sclerosis (SSc), results in high morbidity and mortality. Lung fibroblasts have long been implicated in the progression of pulmonary fibrosis through their activation into myofibroblasts and secretion of excessive ECM. Recently, extracellular vesicles (EV) have been implicated in several diseases. However, characterization of EV during myofibroblast activation in fibrosis has yet to be delineated. We show that activation of primary human lung fibroblasts (phLF) with the profibrotic cytokine Transforming Growth Factor β (TGF-β) reduces the release of EV while increasing their protein content. Similarly, lung tissues from donors whose lungs are not used for transplantation showed a reduction in EV release coupled with an increase in their protein cargo in response to TGF-β. Interestingly, in both lung fibroblasts and tissues, there was no significant change in average diameter of EV released with TGF-β treatment compared to control. To begin characterizing the cargo of EV, we compared levels of a lysosomal cysteine peptidase, Cathepsin L (CTSL), with anti-fibrotic properties in the supernatants of fibroblast and in EVs. We report that despite a significant downregulation of CTSL expression and a corresponding decrease in CTSL secreted levels in the supernatants, TGF-β-activated myofibroblasts increase packaging of CTSL into EVs. This suggests that activated myofibroblasts package CTSL into EV in a paracrine endeavor to inhibit progression of fibrosis and maintain homeostasis. Our future goals include understanding the functional implications of this phenomenon. Our findings provide insights into EV paracrine signaling in the lung and will pave the way for development of EV-mediated delivery of targeted antifibrotic therapies for fibrotic lung diseases.

Alison Mercer-Smith, University of North Carolina – Chapel Hill

Tumor-homing cytotoxic induced neural stem cells as an adjuvant treatment for non-small cell lung cancer brain metastases

Mercer-Smith, A., Jiang, W., Bago, J., Khagi, S., Hingtgen, S.

INTRODUCTION/BACKGROUND: 44% of all brain metastases are due to non-small cell lung cancer (NSCLC). Multifocal brain metastases are typically treated with radiation, but 40% of patients show recurrence. An adjuvant treatment is needed to salvage for disease post-radiation. Neural stem cells (NSCs) home to tumors, and when engineered to secrete cytotoxic TRAIL, they can significantly reduce tumor burden in vivo. To provide an autologous NSC therapy, we transdifferentiated human fibroblasts into induced neural stem cells (hiNSC).

SPECIFIC EXPERIMENTAL AIMS: We aim to characterize the migration of hiNSCs toward multifocal NSCLC disease in the brain and to determine the effect of radiation and secreted TRAIL on NSCLC both in vitro and in vivo.

METHODS/DESIGN: To characterize the migration and persistence of hiNSCs in the brain, we injected hiNSCs intracerebroventricularly (ICV) into mice with bilateral intracranial NSCLC tumors. We used fluorescent analysis of brain sections to characterize migration. To determine the cytotoxic effect of TRAIL and radiation, we performed in vitro co-culture assays and used an isobologram analysis. We investigated the cytotoxic effect in vivo by implanting an H460 tumor in the brains of mice, focally irradiating with 2 Gy, and intratumorally injecting hiNSC-TRAIL. Tumor volume was tracked via bioluminescent imaging (BLI).

RESULTS: Following ICV injection, hiNSCs persisted in the brain >1 week and colocalized to bilateral tumors within that time. Isobologram analysis for the combination of radiation and TRAIL showed a combination index of 0.49, this combination has a synergistic cytotoxic effect on NSCLC. Mice treated with the combination of radiation and intratumoral hiNSC-TRAIL showed 9.42% mean tumor volume compared to controls. Radiation-only and hiNSC-TRAIL-only showed 79.3% and 47.6% mean tumor volumes, respectively. Only mice that received combination therapy demonstrated significant improvement in survival (40%) compared to controls.

CONCLUSION/FUTURE DIRECTIONS: We found hiNSCs can colocalize with multifocal NSCLC tumors in vivo. In vitro TRAIL and radiation have a synergistic killing effect, and in vivo hiNSC-TRAIL and radiation together extended survival. This work demonstrates the therapeutic potential of hiNSC-TRAIL as an adjuvant to radiation. Next steps involve determining the effect of radiation on hiNSC migration and testing the therapeutic efficacy of ICV-infused hiNSC-TRAIL cells after radiation.

Microbiology & Infectious Diseases

Valerio Rasi, Saint Louis University

Mechanistic investigations of Granzyme A-mediated γ9δ2 T cell TB protective effects

Introduction and Background: One fourth of the world population is infected with Mycobacterium tuberculosis (Mtb). Currently, Bacillus Calmette–Guérin (BCG) strains are the only vaccines available to protect against tuberculosis (TB). Our lab has identified γδ T cells that secrete Granzyme A (GzmA) with TB protective effects. GzmA released by TB-specific γδ T cells has been shown to inhibit the intracellular replication of the pathogen.

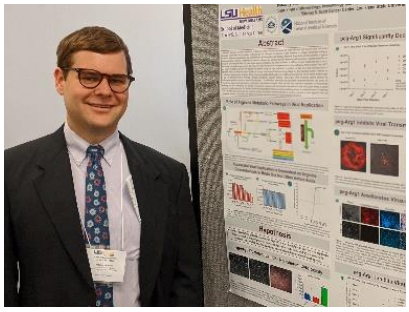
Specific Experimental Aims: To elucidate the mechanism(s) involved in GzmA-mediated mycobacterial pathogen inhibition using a relevant in vitro human system.

Methods and Design: Our lab purified human GzmA to infer species-specific mechanisms. This GzmA was utilized to treat mycobacteria-infected primary monocytes from multiple volunteers, and cell lysates were analyzed for differentially abundant proteins using 2D-DIGE global proteomics. A catalytically inactive GzmA variant was also produced to understand the enzymatic role of this protein in MGIA, and pro-inflammatory marker extracellular TNF was measured. In parallel, confocal microscopy experiments have been conducted to study GzmA internalization and subcellular co-localization within infected monocytes.

Results: We have evidence that Granzyme A's intact active site is necessary to inhibit the intracellular replication of mycobacteria. The substitution of serine to alanine in the active site appears to render the protein unable to control the mycobacterial infection as measured by mycobacterial growth inhibition assays, and the decreased levels of TNF. The 2D-DIGE proteomic approach identified two pathways involved in control of mycobacterial replication using GzmA. This analysis indicates that ER-stress response (HSPA5, HSP90B1, P4HB, PDIA3) and purinergic channel receptor activation (ATP5B/C1/D/H/O) may be important for GzmA-mediated intracellular mycobacterial inhibition. Preliminary confocal microscopy experiments show that GzmA is internalized within the infected cell.

Conclusion and Future Directions: Modulation of key proteins in these pathways are currently being targeted by pharmaceutical intervention and gene alteration to test the effects on GzmA-mediated inhibitory effects. It will be investigated if GzmA co-localizes in these cellular compartments. Confirmation that these pathways are involved in pathogen clearance will lead to the development of novel host-directed therapies for control of Mtb infection.

Nazary Nebeluk, LSU New Orleans



Mechanistic Assessment of the Broad Spectrum Antiviral Effects of Disrupting Host Cell Arginine-Associated Metabolic Pathways Using Adenoviral Infection as a Model

Nebeluk, N., Battaglia, D., Sanchez-Pino, M.D., Ochoa, A., Foster, T.P.

Introduction and Background - Traditionally antivirals have been engineered to disrupt a single viral process essential for viral replication and therefore have had limited therapeutic effectiveness due to restricted viral specificity and subsequent development of drug resistance. As obligate intracellular pathogens, viruses are reliant on host metabolism synthesis pathways to facilitate replication. In particular, the bioavailability of arginine and its metabolites is required for replication of most viral pathogens and initiation of disease-promoting pathophysiology. Arginine metabolites are shunted to pathways critical for viral transcription, genomic replication, and protein synthesis. In addition, arginine metabolism plays a role in maintaining intracellular energy reserves that viruses draw upon. Evaluation of two representative human pathogens, Herpes Simplex Virus (HSV) and Adenovirus (AdV), indicated that arginine was depleted during lytic viral replication. In addition, our data shows that increasing levels of arginine in the extracellular environment significantly increase the amounts of infectious virus produced in a dose dependent manner. Therefore, we hypothesized that therapeutic disruption of host arginine-associated metabolic pathways would have broad antiviral activity across multiple stages of the viral replicative process.

Specific Experimental Aims – 1) To examine the effects of viral infection on host cell amino acid metabolism; 2) To assess the effect of disrupting host arginine metabolic pathway on replication of model viral pathogens; 3) To characterize the underlying mechanisms of action responsible for inhibition of model viral pathogen replication following arginine metabolism disruption.

Methods and Design - Using peg-Arg1 as a tool to deplete extracellular arginine levels we evaluated the effect of this intervention on HSV-1 and ADV5 viral yields along with viral transcription, protein expression, genomic replication and virally mediated cytopathology in vitro.

Results - We observed that peg-Arg1 administration: i) exhibited no cytotoxicity; ii) significantly decreased infectious viral yields; iii) reduced viral transmission; iv) ameliorated virus-mediated cytopathic effects; v) reduced expression of viral proteins; vi) inhibited viral genomic replication and vii) inhibited transcription of early viral genes leading to global decreases in viral transcription.

Conclusions and Future Directions - Our findings illustrate that targeting host arginine-associated metabolic pathways is a potential means of controlling both viral replication and disease. The combined antiviral and disease resolving activities of peg-Arg1 represent a novel approach with vast therapeutic potential. Future studies will further illuminate the antiviral mechanisms of host cell arginine disruption.

Cameron Adams, University of North Carolina – Chapel Hill

Structural Analysis to Understand How Human Antibodies Neutralize Flaviviruses

Cameron Adams, Carbaugh, D., Segovia-Chumbez, B., Graham, S., Diehl, S., Lazear, H., de Silva, AM., Lakshmanane, P.

Introduction and Background: The flavivirus global health burden is exemplified by an estimated 396 million annual dengue virus (DENV) infections and the severe congenital disabilities caused by Zika virus (ZIKV). Primary infection by flaviviruses, including ZIKV, elicits a robust antibody response. However, only a small number of these antibodies can neutralize the infecting virus and confer long-term protection against re-infection. The flavivirus envelope (E) protein is the main target of neutralizing antibodies. E-protein is composed of three domains (EDI, EDII, and EDIII) and forms 90 antiparallel homodimers on the surface of the infectious virion. During viral entry and upon endosomal acidification, E-protein rearranges from dimers to trimers, involving large interdomain conformational changes. Most potently neutralizing human monoclonal antibodies (mAb) target quaternary epitopes that span across E-proteins and are hypothesized to lock the E-protein in the dimer conformation but this hypothesis lacks direct experimental evidence.

Specific Experimental Aims: We isolated a potently neutralizing monoclonal antibody (G9E) (EC50 =1.3 ng/mL) from a patient with primary ZIKV infection and aimed to understand its mechanism of potent neutralization.

Methods and Design: We determined the crystal structure of G9E in complex with recombinant ZIKV E-protein to 3.4 Å resolution. The structure revealed that G9E interaction is predominantly mediated by EDII of one E protein with noticeable peripheral contacts across E-homodimer. We designed structure-based G9E variants with changes to affect G9E binding across the E-dimer.

Results: All G9E variants maintained binding affinity to ZIKV recombinant E-protein dimer similar to G9E WT. G9E variants that altered one or two interactions across the homodimer showed only slight reduction in neutralization. However, a G9E variant (G9E-DNSK) that abrogated the majority of contact across the homodimer reduced in-vitro neutralization potency by >100-fold.

Conclusions and Future Directions: These new structural insights into how antibodies mediate potent neutralization indicate importance of eliciting antibodies that bind across Flavivirus E-protein dimers. This knowledge can aid in rational vaccine design of next generation of Flavivirus vaccines.

General Medicine II

Lauren Clai Morehead, University of Arkansas

Caloric restriction mimetics as an adjuvant to immune checkpoint inhibitors for treatment of melanoma

Morehead LCE, Wallis KF, Tackett AJ, Miousse IR

Introduction and Background

Immune checkpoint inhibitors (ICIs) have revolutionized melanoma therapy. Still, the 5-year survival for advanced melanoma is only 50%. This leads to two questions: what makes some tumors less responsive to ICIs, and what can be done to increase responsiveness? Prior research suggested that hypoxia in the tumor microenvironment (TME) decreased the efficacy of ICIs, and metformin, an antihyperglycemic and caloric restriction mimetic (CRM), was able to reverse this condition. We hypothesized that other CRMs will also increase responsiveness to CRMs by decreasing hypoxia. We chose three other CRMs to study alongside metformin: hydroxycitrate, resveratrol, and sulforaphane.

Specific Experimental Aims

Aim 1: Compare the effect of sulforaphane, hydroxycitrate, and resveratrol with metformin on in vivo tumor growth and hypoxia.

Aim 2: Determine the mechanism by which CRMs decrease oxidative phosphorylation in melanoma cells.

Methods and Design

Proteomics analysis was done with a tandem mass tag labeling in the B16F10 murine melanoma cell line. Oxygen consumption rate and acidification rates were measured on a Seahorse instrument. To determine effect of caloric restriction mimetics on immunotherapy efficacy, B16F10 cells will be injected subcutaneously in immunocompetent male and female C57BL/6J mice, separated into four groups: 1) no treatment control, 2) ICI therapy only, 3) CRM therapy only, 4) ICI + CRM combination.

Results

Caloric restriction mimetics inhibit the growth of both murine B16F10 and human A101D melanoma cells. We calculated IC50s for each compound to use in a proteomic screen. Twenty-two proteins were significantly up-/down-regulated by all four compounds in the B16F10 cell line. Our Seahorse data indicate that all four mimetics significantly down-regulate oxidative phosphorylation.

Conclusions and Future Directions

Our preliminary data shows that, like metformin, additional CRMs decrease oxidative phosphorylation in cancer cells. This supports the hypothesis that CRMs are beneficial in increasing responsiveness to ICIs by decreasing hypoxia. We started testing the effect of four CRMs on tumor growth and hypoxia in an animal model. Our ultimate goal is to improve responsiveness to immune checkpoint inhibitors in patients with metastatic melanoma.

Anuj Tharakan, Virginia Commonwealth University

Transcriptomic profiling of migratory conventional dendritic cells during allergic sensitization

Anuj Tharakan and Rebecca K. Martin

Introduction and Background: Anaphylaxis is a type of severe allergic reaction caused by cross-linking of high-affinity IgE on mast cells leading to mast cell degranulation. Production of anaphylactic, high affinity IgE is induced a population of T lymphocytes called T follicular helper 13 (Tfh13) cells. The mechanisms regulating the polarization to the Tfh13 fate, however, are unclear.

Specific Experimental Aims: We hypothesized that dendritic cells migrating from the pulmonary mucosa to draining lymph nodes following exposure to Tfh13 inducing and non-Tfh13 inducing stimuli would exhibit distinct migratory patterns and transcriptional profiles.

Methods and Design: To determine T cell polarization induced by each adjuvant, WT mice were immunized and challenged with ovalbumin (OVA)+LPS, papain, or Alternaria. T cell polarization was determined by cytokine production in mediastinal lymph nodes (mLNs) and flow cytometry. To monitor DC migration, WT mice were immunized intranasally with AlexaFluor647-conjugated OVA alongside the adjuvants LPS, papain, or Alternaria. 6-48 hours post immunization, mice were euthanized and single-cell suspensions were generated from mediastinal lymph nodes (mLN). These cells were then stained for flow cytometric analysis. For RNA-seq analysis, migratory DCs were isolated from mLNs by fluorescence-activated cell sorting 18-24 hours post immunization. Total RNA was isolated and used to generate a cDNA library. Sequencing was conducted on the Illumina HiSeq platform using paired-end 150bp reads.

Results: LPS induced Th1, Th17, and Tfh1 polarization, papain induced Th2 polarization, and Alternaria induced Th2 and Tfh13 polarization. Analysis of DC migration following immunization with the LPS, papain, and Alternaria revealed markedly different migration kinetics following each stimulus. However, numbers migratory Ag+ DCs, amount of antigen uptake, and expression of co-stimulatory molecules were similar between all groups. RNA-seq analysis of these migratory DCs demonstrated unique transcriptional profiles induced by each adjuvant. We found that, following Alternaria exposure, migratory DCs upregulated genes involved in autophagy and mitophagy while downregulating genes involved in the mitochondrial electron transport chain compared to LPS or papain exposure.

Conclusions and Future Directions: These results indicate that each adjuvant induces differential activation of pulmonary DCs, leading to the induction of distinct signaling pathways and transcriptional responses. These differences may be responsible for differential T cell polarization in response to these adjuvants. In future experiments, we will use pharmacological inhibitors of these pathways using an in vivo T cell polarization screening system to identify which, if any, of these pathways are critical for Tfh13 polarization.

Maya Lozinski, University of Chicago

Risk Adjustment is Inaccurate for Complex Patients because Health Conditions have Increasing Marginal Effects

Introduction and Background: Risk adjustment is used to adjust outcomes predictions for individuals' health characteristics in research, quality measurement and insurance markets. However, current risk adjustment models consistently misestimate outcomes, including costs, for multi-morbid patients. These inaccuracies have impaired efforts at quality measurement, research inference, and payment reform. Previous work has focused on the role of omitted variables bias in causing these inaccuracies. This project proposes and evaluates another potential explanation: incorrect functional form assumptions.

Specific Experimental Aims: Most risk adjustment models assume that a health condition affects outcomes the same amount for every person, i.e. has a constant marginal effect. However, the marginal effect of a health condition may increase in the presence of other health conditions. For example, diabetes is more costly in the presence of depression; Covid-19 is more severe in the presence of kidney disease. If true, this pattern can explain why current risk adjustment models misestimate outcomes for multimorbid patients. This research aims to test if this pattern is present in healthcare data, with a focus on cost predictions.

Methods and Design: I look for evidence of increasing marginal effects on costs in the Truven Marketscan Commercial Claims Data 2014-2015 (n=9,574,907). I estimate a standard risk adjustment model similar to models used by many researchers and by Medicare to determine Part C premiums. I also calculate an empirical marginal effect using exact matching. I then compare model and empirical marginal effects.

Results: The 50 most common health conditions all display increasing marginal effects in the number of health conditions. In addition, the distribution of health conditions per person is highly skewed right. As a result, the risk adjustment model substantially underestimates the marginal effect a few highly morbid individuals and modestly misestimates the effect for many relatively healthy people.

Conclusions and Future Directions: Functional form assumptions must be relaxed to generate unbiased predictions for multi-morbid patients. Future work will focus on developing risk adjustment models which allow for heterogenous marginal effects.

Neuroscience

Carolyn Kaufman, University of Kansas

Aerobic exercise improves hippocampal blood flow for hypertensive Apolipoprotein E4 carriers

Kaufman, C.S., Honea, R.A., Pleen J., Lepping R.J., Billinger S.A., Burns J.M., Vidoni E.D.

Introduction and Background: Evidence increasingly suggests cerebrovascular dysfunction plays an early and important role in the pathogenesis of Alzheimer's disease (AD). Studies have shown the strongest known genetic risk factor for sporadic AD, Apolipoprotein E4 (ApoE4), may act synergistically with vascular risk factors to promote dementia development. Aerobic exercise may attenuate cognitive decline at least partially through improvements in cerebral blood flow. Therefore, exercise interventions that improve vascular health may be particularly beneficial for ApoE4 carriers.

Specific Experimental Aims: To compare between ApoE4 carriers and non-carriers 1) the change in hippocampal blood flow (ΔHBF) after an aerobic exercise intervention and 2) the relationship between the change in MAP (ΔMAP) and ΔHBF.

Methods and Design: In a randomized controlled trial, we assigned cognitively-normal older adults (65–87 years) to a 52-week aerobic exercise intervention or education only. For this secondary analysis, we selected only participants with elevated blood pressure at the time of enrollment (N = 41), defined as mean arterial pressure (MAP) greater than 93 mmHg. We measured cerebral blood flow using arterial spin labeling magnetic resonance imaging before and after the 52-week intervention. Genotyping was performed by LCG Genomics using KASP proprietary genotyping technology.

Results: A two-way ANCOVA showed a significant interaction between ApoE4 carrier status and treatment group (exercise or control) on ΔHBF, even when controlling for age ($p = 0.026$). For ApoE4 carriers, ΔHBF was significantly higher for participants who underwent the exercise intervention (4.667 mL/100g/min) than for the control group (-3.361 mL/100g/min), a difference of 8.028 ($p = 0.005$). There was no difference in ΔHBF between the control (-0.118 mL/100g/min) and exercise (-0.901 mL/100g/min) intervention groups for ApoE4 non-carriers ($p = 0.773$). Additionally, a multiple linear regression showed a significant interaction between ΔMAP and ApoE4 carrier status on ΔHBF ($p = 0.010$), with a reduction in MAP correlating with an increase in HBF for ApoE4 carriers only.

Conclusions and Future Directions: Aerobic exercise significantly improved HBF for ApoE4 carriers only. Additionally, only ApoE4 carriers exhibited an inverse relationship between ΔMAP and ΔHBF. This suggests exercise interventions, particularly those that lower MAP, may be beneficial for individuals at highest genetic risk of AD.

Anna Giarratana, Rutgers University

The Role of Genetic Polymorphisms in a Mouse Model of Traumatic Brain Injury and Personalized Treatment Approaches

Anna Giarratana, Shavonne Teng, Sahithi Reddi, Cynthia Zheng, Smita Thakker-Varia, Janet Alder

Introduction and Background: Traumatic Brain Injury (TBI) is a serious and potentially life threatening problem. Clinicians have long noticed that certain patients recover better after TBI and we seek to identify genetic differences underlying these differences. This knowledge can be used to explore precision medicine approaches to treatment.

Specific Experimental Aims: 1. To investigate cellular and behavioral outcomes in genetically engineered mice with the BDNF Val66Met and ApoE4 polymorphism following repeated, mild TBI (rmTBI) in a lateral fluid percussion injury (LFP) model in order to determine if these genetic polymorphisms are risk factors for poor recovery after rmTBI. 2. To develop precision medicine treatment approaches to any vulnerabilities discovered.

Methods and Design: We used a LFP rmTBI model in order to order to create replicable injuries similar to those seen in the majority of human TBI cases. In order to analyze outcomes after injury, we used magnetic resonance imaging (MRI), immunohistochemistry, western blot, and behavioral assays.

Results: We found that injured Val66Met and ApoE4 carriers have a larger injury volume as assessed by MRI relative to injured Val66Val and ApoE3 carriers. We have shown that injured Val66Met carriers have increased levels of neurodegeneration, apoptosis, p-tau, activated microglia, and gliosis in the cortex and/or hippocampus compared to injured Val66Val carriers at 1 and/or 21 days post injury (DPI) and that injured ApoE4 carriers have increased levels of neurodegeneration, apoptosis, activated microglia, and p-tau in the cortex and/or hippocampus compared to injured ApoE3 carriers at 1 and/or 21 DPI. We have also found that injured Val66Val mice have significantly more total BDNF than injured Met carriers. In the hippocampus at 1 DPI and 21 DPI, we found that injured Met carriers have more proBDNF/mature BDNF than the injured Val66Val carriers. In the ApoE mice, we found that ApoE3 injured mice have more total BDNF than ApoE4 injured mice at 1 and 21 DPI in both the cortex and the hippocampus.

Conclusions and Future Directions: Therefore, we have concluded that Val66Met and ApoE4 are risk factors for poor outcomes after rmTBI. For precision medicine treatment approaches, in the Val66Met injured mice we used an AAV-BDNF virus to overexpress wildtype BDNF, while in the ApoE4 injured mice we used Bryostatin-1, a PKCε activator that has previously been shown to increase BDNF levels. AAV-BDNF treatment in Val66Met injured mice reduces astrogliosis and activated microglia at 21 DPI and increases learning and memory. Bryostatin-1 treatment in the ApoE4 injured mice reduces neurodegeneration and activated microglia at 1 DPI and improves recovery in learning and memory. This study highlights the role that precision medicine treatment approaches may be able to play in recovery for susceptible individuals.

Deborah Rupert, Stony Brook University

The Role of MeCP2 in Auditroy Cortex Inhibitory Interneurons for Processing Ultrasonic Vocalizations

Rupert, D. and Shea, S.

Background: Autism Spectrum Disorders (ASD) and Rett Syndrome (RTT) are characterized by impaired communication. RTT is a pervasive, neurodevelopmental disorder previously classified as an ASD and caused by loss of function mutations in the X-linked gene MeCP2.

Objectives: Our goal is to determine the contribution of Mecp2 mutation to disruptions of auditory cortical circuitry and plasticity that degrade social vocal perception in a mouse model of Rett syndrome.

Methods: To achieve this goal, we will use a circuit-specific Mecp2 mutant mouse model in combination with a behavioral paradigm that relies on vocal communication. We employ pup retrieval in response to ultrasonic vocalizations (USVs)- a natural, auditory-dependent, learned maternal behavior that we report to be impaired by Mecp2 mutation. USVs are highpitched distress calls emitted by isolated infant pups that trigger a retrieval response in wild-type but not non-conditional, Mecp2 heterozygous females. Our previous work suggests that this difference is the result of impaired plasticity in the auditory cortex (ACtx) of Mecp2 mutant animals, a brain region required to detect and interpret vocalizations. ACtx inhibitory interneurons seem to be especially important for processing of socially relevant stimuli (e.g. USVs). Here we build on these findings by selectively inhibiting transcription of Mecp2 protein in a specific subclass of inhibitory interneurons- those expressing the calcium-binding protein parvalbumin.

Results: We examine the effects of restricted Mecp2 mutation in parvalbumin positive (PV+) inhibitory interneurons on pup retrieval behavior and in vivo neural circuit activity in the ACtx in response to socially relevant auditory stimuli. We have found Mecp2 mutation restricted to this cell type is sufficient for impairing pup retrieval behavior. Further, we found ACtx cellular responses to pup vocalizations are altered in “PV-Mecp2” mutants compared to WT controls. These differences are specific to socially relevant sounds (i.e. USVs) as opposed to pure tones.

Conclusions: This work focuses on functional consequences of Mecp2 mutation in auditory processing circuitry that expands our understanding of the underlying etiology of RTT, identifies targets for ameliorating the downstream consequences, and informs pathophysiological mechanisms underlying neurodevelopmental disorders more broadly.

Student Poster Session I

Alex Casella
University of Maryland Baltimore
Regulome-wide association study identifies transcription factor networks associated with risk for schizophrenia.

Alexandra Goetjen
University of Connecticut
GABRA2 genetic variants and chromatin accessibility in induced pluripotent stem cell-derived neural cells and postmortem brain samples in the context of alcohol use disorder

Alice Tang
University of California San Francisco
Deep Clinical Phenotyping and Network Analysis of Alzheimers Disease Patients Leveraging Electronic Medical Records Data

Anne Wells
University of Texas San Antonio
Topological Analysis of Connections between Hypothalamus and Prefrontal Cortex in Adult Rhesus Monkey

Annica Stull-Lane
University of California, Davis
Non-typhoidal Salmonella that causes invasive disease evades reactive oxygen species production by neutrophils

Anthony Hung
University of Chicago
Characterizing inter-individual variation in gene expression responses using an in vitro model of osteoarthritis

Ashley Guest
University of Arizona
Neural firing rate in the subthalamic nucleus does not change during ipsilateral deep brain stimulation

Austin Jolly
University of Colorado
Epigenetic control of pathological vascular remodeling: Role of smooth muscle-derived AdvSca1-SM progenitor cell induction of HDAC9-Brg1

Bejan Saeedi
Emory University
Behind the Microscope: Lessons from the People and Process of Science and Medicine

Brett Colbert
University of Miami
Expression of Hearing Loss Related Genes in iPSC Derived Cells of the Human Inner Ear

Cameron Adams
University of North Carolina Chapel Hill
Structural Analysis to Understand How Human Antibodies Neutralize Flaviviruses

Camila Villasante
Cornell University
Elucidating the elastic properties of the protocadherin 15 dimer, a critical mediator of human hearing

Caroline Jansen
Emory University
CD8 T-cell infiltration into renal tumors is maintained by a stem-like CD8 T cell, requires an intratumoral supportive antigen presenting niche, and is independent of PD-L1 status

Carolyn Kaufman
University of Kansas
Aerobic exercise improves hippocampal blood flow for hypertensive Apolipoprotein E4 carriers

Carson Wills
Pennsylvania State University
Chemotherapy Promotes Breast Cancer Metastasis Through Extracellular Vesicle Secretion

Connor Hughes
University of Colorado
Investigating the role of Eya3 in regulation of innate immune signaling cascades in TNBC

David Basta
University of Southern California
Heat-shock proteases delay bacterial aging

Dylan Eiger
Duke University
Biased Agonism at CXCR3 Drives Differential Phosphoproteomic and Transcriptomic Profiles and Cellular Outputs

Emily Przysinda
University of Rochester
Neural Differences in theory of mind network during socially awkward events in schizophrenia

Esther Choi
Pennsylvania State University
Molecular interactors of toxic SOD1 trimers in ALS pathophysiology

Evan Tracy
University of Louisville
Coronary Microvascular β1 Adrenergic Receptor Dysfunction is Associated with Oxidative Stress, Reversible by Adipose Stromal Vascular Fraction Injection in Aged Female Rats

Frederick Damen
Purdue University
High Frequency Four-Dimensional Ultrasound (4DUS): An In Vivo Foundation for Assessing Murine Cardiac Biomechanics

Graeme Murray
Virginia Commonwealth University
Single cell biomass tracking enables identification and isolation of therapy resistant cells in a heterogeneous cancer cell populations

Hannah Turbeville
University of Mississippi
Nitric oxide and oxidative stress pathways do not contribute to sex differences in renal injury and function in Dahl SS/Jr rats

Jasmine Geathers
Pennsylvania State University
Fibulin-3 Mutation causes RPE dysfunction in mice and induces UPR and EMT marker expression in vivo

Jennifer Cheung
SUNY Upstate Medical University
Testing novel antiviral compounds in HCMV-infected peripheral blood monocytes

Jerricho Tipo
University of Texas Galveston
Investigating the Role of the Glycogen Synthase Kinase 3 Pathway in the Pathophysiology of Schizophrenia via Qualitative Analysis of FGF12 expression in the Soma of hiPSC Neurons

Joe Mouawad
Medical University of South Carolina
Induction of fibrosis in lung tissues and fibroblasts results in decreased free anti-fibrotic proteins with a corresponding increased packaging in extracellular vesicles.

Kevin Lin
University of Minnesota
Predicting biological function of chemical compounds through CRISPR-Cas9 chemical-genetic screens

Kristin Weeks
University of Iowa
Gynecologic Oncologists Impact on Adjuvant Chemotherapy Care for Ovarian Cancer Patients: A Cohort Study of the Midwestern United States

Kyle Woisard
Virginia Commonwealth University
Within-executive control network resting state fMRI functional connectivity in opioid use disorder

Luke White
Louisiana State University Shreveport
Development and Feasibility Testing of a Basic Emergency Plug and Play Ventilator

Maryknoll Palisoc
Pennsylvania State University
Elucidating PIK3CA-Cooperating Mutations in Breast Cancer Using an Inducible and Mammary-Specific Transposition Mutagenesis System

Matthew Ryan
University of California San Francisco
A functional genomic approach to interrogate hormone dependence and tumor evolution in prostate cancer

Narayana Yelleswarapu
Michigan State University
Enteric neuronal aggregation of alpha-synuclein disrupts colonic propulsion

Nikki Barrington
Rosalind Franklin University
Persistent upregulation of brain phospho-tau is accompanied by elevated hippocampal synaptic excitability and altered Ca2+ handling, following single or repeated closed-head concussive impacts

Nozima Aripova
University of Nebraska
Fibrinogen Modified with Malondialdehyde-Acetaldehyde (MAA) and/or Citrulline (CIT) Induce Pro- inflammatory and Pro-fibrotic Responses

Oleg Makarevich
University of Maryland
Mithramycin selectively attenuates DNA-damage-induced neuronal cell death

Olivia Uddin
University of Maryland
Parabrachial Nucleus in Migraine Pain

Oygul Mirzalieva
Louisiana State University
Characterization of MUL1, a Ubiquitin Ligase Involved in Mitochondrial Recycling

Renee Wu
Washington University St. Louis
cDC1 prime and are licensed by CD4+ T cells to induce anti-tumor immunity

Ryan Chow
Yale University
The aging transcriptome and cellular landscape of the human lung in relation to SARS-CoV-2

Safwan Elkhatib
University of Nebraska
Sympathetic splenic denervation ameliorates psychological trauma-induced inflammatory and redox shifts in T-lymphocytes

Sai Suma Samudrala
University of Nebraska
Patient-specific iPSCs to Model Ebstein's Anomaly (EA) with Left Ventricular Non-Compaction (LVNC)

Shuyan Qin
University of Rochester
Reverse Abscopal Effect: Presence of Immunologically Cold Tumor Confers Immune Resistance to Immunologically Hot Tumor in Synchronous Melanoma

Sylvia Edoigiawerie
University of Chicago
Comparing Amplitude Integrated Electroencephalography to Teager-Kaiser Energy-derived Algorithm for Neonatal Seizure Detection

Tiffany Kaul
Tulane University
Insights into the regulation of expressed LINE-1 mobile elements

Tina Zheng
University of California San Francisco
Human pluripotent stem cell models of high-risk neuroblastoma

Vishnu Rao
University of Maryland
Metabolic Coupling of Pancreatic Beta Cells and the Coordination of Islet Activity

Yueqi Ren
University of California, Irvine
Characteristics of high-frequency oscillations in intracranial electroencephalography depend on electrode type

Student Poster Session II

Aditi Misra
University of Rochester
Cellular Contributions to Neonatal Regeneration

Alan Finkelstein
University of Rochester
Alterations in Network Topology and Cognition After Radiotherapy

Alanna Kaplan
Yale University
Cediranib directly suppresses homology-directed DNA repair through downregulation of BRCA1/2 and RAD51

Alexander Baez
Stony Brook University
SAPAP3 Knockout Model of OCD Leads to Differences in Striatal Cholinergic Interneurons

Alexander Verma
University of South Dakota Sanford
Lactate Induces PD-L1 in HRASG12V-positive Oropharyngeal Squamous Cell Carcinoma

Alicia Ivory
Medical College of Wisconsin
The Role of Estrone, Estradiol and G Protein Coupled Estrogen Receptor in Endothelial Progenitor Cell Function

Alison Jarmas
University of Cincinnati
Identification of mechanisms regulating mammalian nephron endowment

Amin Izadpanah
Tulane University
The Role of Stem Cells in Breast Tumor Microenvironment

Ashley Bolte
University of Virginia
Meningeal Lymphatic Dysfunction Exacerbates Traumatic Brain Injury Pathogenesis

Brandon Rosen
University of Miami Miller
Rhesus Cytomegalovirus-Specific CD8+ Cytotoxic T Lymphocytes Do Not Become Functionally Exhausted in Chronic SIVmac239 Infection

Brian Upton
University of Cincinnati
Encephalopsin (OPN3) in the Developing and Adult Central Nervous System

Briana Wilson
University of Virginia
Rapid destabilization of trailer derived tRNA fragments (tRF-1s) by RNases blocks entry of tRF-1s into RISC

Carlie Aurubin
Medical College of Wisconsin
The Tale of Two Receptors: Determining the role of lipoprotein receptors, SR-BI and LDL-R, in gammaherpesvirus infection

Carol Upchurch
LSU New Orleans
Implementing a Markov Model of Nav1.6 into a morphologically realistic model of a CA1 Hippocampus Pyramidal Cell to Simulate Adaptive Firing in Place Fields

Chloe Cavanaugh
Rutgers Robert Wood Johnson Medical School/ Princeton University
Mechanism and Therapeutic Implications of Host Telomerase Modulation by Human Cytomegalovirus

Elizabeth Higginson
Michigan State University
Sex differences in hippocampal physiology: Circuit-specific mechanisms underlying stress susceptibility

Elorm Agra
Emory University
Papillary muscle approximation (PMA) at the tips rather than bases improves systolic mitral valve geometry correcting functional mitral regurgitation in an ex vivo porcine heart benchtop model

Eulanca Liu
UC San Diego
Detecting changes in brain state with a toolbox of noninvasive, quantitative functional magnetic resonance imaging (fMRI) techniques

Francisco Neal
University of Texas Health San Antonio
Investigating contributions of the BRCA2 C-terminus to DNA repair by homologous recombination

Hannah Knochelmann
Medical University of South Carolina
IL-6 is critical for Th17-mediated memory responses to tumors

Jacob Elnaggar
LSU New Orleans
Use of Shotgun Metagenomics To Investigate The Pathogenesis of Incident Bacterial Vaginosis

Jacob Meariman
LSU New Orleans
Nalfurafine Produces a Pertussis-Toxin Sensitive Water Diuresis via the Kappa Opioid Receptor

Jamarius Waller
University of Mississippi
DETERMINING THE EFFECTS OF PRO-ANGIOGENIC ELP-VEGF- A THERAPY ON TUMOR GROWTH AND PROGRESSION

James Fisher
UTMB
Pattern recognition receptor Mincle senses Orientia tsutsugamushi: a potential mediator of polarized innate responses in scrub typhus

Jesse Wang
University of Rochester
A Patient-Centered Digital Scribe for Automatic Medical Documentation

Jesus Zamora-Pineda
Loyola University Chicago
Immune Tolerance Induction by the Exopolysaccharide from the Probiotic Bacillus subtilis

John Flickinger
Thomas Jefferson University
Peptide-MHC-Stabilizing Modifications Rescue Subdominant Vaccine- Directed CD8+ T-cell Responses in Listeria Monocytogenes-based Vaccines

John Yuen
Stony Brook University
Development of 5-FU modified tumor suppressor miRNAs as a platform for miRNA based cancer therapeutics

Josh Barton
Thomas Jefferson University
GUCY2C regulates appetite through leptin-dependent hypothalamic neurons

Karl Foley
University of Rochester
Early developmental arsenic exposure alters hippocampal synaptic transmission in mice

Keshov Sharma
University of Rochester
A Specific Projection from the Amygdala to Auditory, Visual, and Multisensory Sites in the Ventrolateral Prefrontal Cortex of the Macaque

Laura Marquez Loza
University of Iowa
LENTIVIRAL VECTOR OPTIMIZATION FOR CYSTIC FIBROSIS GENE THERAPY

Leanne Dumeny
University of Florida
Association of SLC5A2 Polymorphisms with Cardiovascular Outcomes in Heart Failure Patients

Mallory Peterson
Penn State University
Pediatric Neural MRI Segmentation Toolbox

Manasi Malik
Washington University in St Louis
Genetic variants alter oxytocin receptor localization and signaling

Margaret MacGibeny
Rutgers Robert Wood Johnson Medical School
Bacteria but not viruses are distinguishable in cutaneous T-cell lymphoma skin microbiome versus healthy controls

Meghan Kellett
University of Colorado
Investigating the role of nuclear FAK to promote angiogenesis in Thyroid Cancer

Nate Diehl
UNC Chapel Hill
Life without KRAS: profiling the KRAS-dependent kinome to identify novel therapeutic vulnerabilities in pancreatic cancer

Patricia Yee
Penn State
Hyperactivating the Hippo pathway effector TAZ differentially distorts the tumor microenvironment, promotes tumor-associated neutrophil infiltration, and phenocopies mesenchymal-glioblastoma

Patrick O'Connell
Michigan State University
SLAMF7 signaling reprogram T cells towards exhaustion in the tumor microenvironment

Saara-Anne Azizi
University of Chicago
Towards chemical probes against zDHHC proteins

Sangwoo Han
University of California, Irvine
Cerebral blood flow, oxygenation, and metabolism immediately prior to cardiac arrest can predict neurological recovery after resuscitation.

Shakoora Sabree
UNIVERSITY OF IOWA
Evaluating the complexity of the immune response to CMP-001, a TLR9 agonist

Shannon Eriksson
Duke University
Extending SABRE hyperpolarization techniques towards in vivo metabolic imaging

Shannon Weber
MUSC
R-Ras Subfamily Proteins Elicit Distinct Physiologic and Phosphoproteomic Effects in NF-Null MPNST Cells

Shree Bose
Duke University
Investigating the Metabolic Reprogramming of Ovarian Tumors During Omental Metastasis

Spencer Katz
Penn State
Silver Deposition MicroCT as a Quantitative Assay for Zebrafish Pigmentation

Taylor Yamauchi
University of Colorado
Investigating the functional organization of cerebellotectal projections in orienting behavior

Thao Trinh
Indiana University
Leptin Receptor as a Marker for Functional Long-term Repopulating Hematopoietic Stem Cells

Yuxing Xia
University of Florida
Tau Phosphorylation of Ser208 Promotes Aggregation of Wild Type tau in Alzheimer's disease and Other Tauopathies

FAQ

How will the virtual conference be different than the in-person conference?

First, do not worry. Like previous years, you **will still receive our conference swag** – this year's awesome water bottle! **To receive this, please register before September 1st.** Second, our planning team has been working around the clock to make sure that this meeting offers the same professional content as the original meeting. There will still be **five keynote speakers** with **live Q&A sessions**. There will also be **breakout sessions** where you can learn skills to succeed as a physician-scientist.

For career-oriented students, we will have the same **Career Panel** and **PSTP Panels** that were offered at the original conference to learn about the many career options available to MD/PhDs. These will have a live, monitored Q&A. In addition, you can reach out to the career panelists via email to schedule individual zooms on our Socio platform! Lastly, we have **individual/small-group PSTP sign-ups** to directly network with PSTP directors from all over the country!

For students looking to showcase your work, there **will still be student poster and oral presentations**. Poster sessions will be streamlined so that each poster can get feedback in the form of emails or zoom rooms. **Poster sessions** can also include a **quick 1 minute video** to increase traffic! **Student oral presenters will still give 12 minute talks followed by live Q&A!**

While we will not be able to offer you our fantastic conference food, we will **subsidize your lunch** on the days you do come to the conference with DoorDash meal cards at $10/day, $40 for the entire conference! Register by September 1st to be eligible for DoorDash coupons! Unfortunately, we will not be able to make the hikes virtual (unless you want to watch a member of our team struggle up the hill), but we will have other fun events!

What will I get out of this meeting?

- Five **Keynote speakers** with live Q&A sessions
- Breakout sessions to learn about Ethics, Health & Wellness, and Interfacing with Industry.
- A breakout session on diversity to discuss strategies and solutions to increase diversity and inclusion. The hope is to create an implementable product to bring back to our institutions and enact change!
- Thinking about how to enact more equitable reform for your school? We are hosting a session **to share ideas and discuss how best to address and enact changes to systemic racial discrimination at schools!**
- **Career Panel Q&A** and **PSTP Panel Q&A**
- Individual meetings with career panelists and PSTP panelists
- Chance to present in our **student oral presentations** (12 minutes talks + 5 minutes live Q&A)
- Submit abstracts to be in consideration for **posters and oral presentations!**
- **Socio connections are forever!** You can reach out to those you met during the conference using the App or via the emails they used to register for the event.
- **Free DoorDash coupon every day you attend the conference ($10/day) - Register by September 1st!**
- Conference swag – this year's water bottle (register by September 1st!)

How do I register? How do I change my registration info and edit an abstract?

Click **here** to register now! Register before **September 1st** to enjoy our conference water bottle swag and complimentary DoorDash coupons! Submit abstract by **August 7th** to be in consideration for oral presentations and by **September 1st** to be in consideration for poster presentations.

Click **here** to claim your registration account. You will be able to edit your registration information and add/edit your abstract submission. Refer to **"How to edit my Registration"** for instructions on claiming your registration account, changing registration info, and editing abstract submissions.

Why the registration cost and where is the money going?

After hard deliberation, we decided that in order to provide for you the same value as the in-person conference we would have to charge for the conference. The registration cost of $150 goes towards the **cost of running this virtual conference**. A portion of the registration cost goes **towards diversity awards to increase inclusivity and diversity for this and future conferences**. If you are an **under-represented minority** or come from a **disadvantaged background**, **please apply for the diversity awards by submitting an abstract by September 1st, 2020.** Lastly, the registration cost goes towards the various benefits you will gain from joining the conference – **swag and subsidized DoorDash meals**.

Networking is a huge aspect of the conference. How will this happen virtually?

We understand that networking is fundamental to conferences, especially for student conferences. The need for networking is precisely why we chose **Socio**, a platform *made* for social encounters, as our virtual platform and partner. In addition, we have worked hard to make sure that there are many social opportunities throughout the conference:

- **Socio connections last forever**. As long as you have the app, you can reach out to attendees from this conference and share connections.
- There are **live Q&A sessions** so students can interact with presenters.
- We have introduced **individual PSTP sessions** so you can meet with PSTP directors just like you would eating at a table in our in-person conference.
- Socio allows you to put **individualized methods of contact**, including sharing your email or your **own personal zoom link/zoom room**.
- We will have **virtual party sessions** and **happy hours** scattered throughout the conference days!

How to access and navigate Socio?

We will be using Socio as our virtual conference event platform. All the video streaming, networking, engagement, and much more offered throughout the conference will be powered by Socio.
We will provide you with further instructions on how to access Socio a few days before the start of the conference. Please remember to check your registration email account!
Check out our "Socio Web App Tutorial" and our "Socio Phone App Tutorial" for instructions on how to navigate Socio (both on your computer AND your phone!) and all that our conference offers!

What is the Diversity Award and how do I apply?

The annual national MD/PhD conference is dedicated to making the event available for **all** MD/PhD students throughout the country. We believe having a more diverse population at the conference will benefit every student in training. **To achieve that end, students from an under-represented minority or from a disadvantaged background (according to NIH standards) may qualify for a diversity award**. In years past, 10 awards were granted, but given the virtual conference of this year, **we have increased the slots to 65.**

To apply, **register and submit an abstract by September 1st** and select "Consideration for Diversity Award". If selected, you will receive a **100% refund** on your registration cost. Please refer to the Diversity Award Guidelines document for guidelines regarding award eligibility and instructions.

How do I submit my poster or oral presentation?

To submit your **poster**, click **here** to access survey and upload file. Or scan this QR code!

For student **oral presentations**, our talk list has been finalized (see roster in *"Student Talks"* section below!). ***Congratulations!*** You should have been contacted to fill out a survey and upload files. Contact us at **MDPhDConference@ucdenver.edu** for any questions!

Conference Student Attendees Roster

Columbia University
Charles Emala

Cornell Tri-Institute
Briana Christophers
Camila Villasante

Duke University
Shree Bose
Jamie Courtland
Rui Dai
Dylan Eiger
Shannon Eriksson
Jennifer Jenks
Arvind Konkimalla

Emory University
Elorm Agra
Danielle Cicka
Caroline Jansen
Bejan Saedi

Icahn Mt. Sinai
William Zhao

Indiana University
Thao Trinh

Johns Hopkins University
Annie Wu

Keck USC
David Basta
Jonathan Fox

USC-Caltech
Blade Olson

LSU New Orleans
David Basta
Jonathan Fox
Oygul Mirzalieva
Nazary Nebeluk
Carol Upchurch
Luke White

Loyola University
Jesus Zamora-Pineda

Mayo Clinic
Kenneth Valles

Medical College of Wisconsin
Carlie Aurubin
Alicia Ivory
Sai Suma Samudrala

Medical University of South Carolina
Hannah Knochelmann
Joe Mouawad
Amer Toutonji
Shannon Weber

Michigan State University
Elizabeth Higginson
Patrick O'Connell
Narayana Yelleswarapu

Northwestern Feinberg
Samantha Schroth

NYU
Xinruo Guo
Laura McCulloch

Penn State
Carrie Barnum
Gregory Brown
Stephen Chih
Esther Choi
Brianna Evans
Jasmine Geathers
Daniel Goetschius
Timothy Helmuth
Martin Johnson
Spencer Katz
Chachrit Khunsriraksakul
Kristin Lambert
Natella Maglakelidze
Kyra Newmaster
Maryknoll Palisoc
Mallory Peterson
Andrew Sugarman
Carson Wills
Patricia Yee

Purdue University
Frederick Damen

Rosalind Franklin University
Nikki Barrington

Rutgers University
Chloe Cavanaugh
Anna Giarratana
Barry Li
Margaret MacGibeny
Evan Waldron

Saint Louis University
Valerio Rasi

Stanford University
Avin Veerakumar

Stony Brook University
Dhivyaa Anandan
Khalayi Martha Aywa
Joseph Bae
Alexander Baez
Anthony Chesebro
Jay Gupta
Tiffany Kim
Joshua Kogan
Kathryn Larkin
Deborah Rupert
Cuilee Sha
Lucia Yang
Kyungyoon Yoo
John Yuen
Camelia Yuejiao Zheng

SUNY Upstate Medical University
Kyle Alpha
Jennifer Cheung
Laura Szczesniak

Texas A&M
Bradley Eckelmann

Thomas Jefferson University
Josh Barton

John Flickinger

Tulane University
Amin Izadpanah
Tiffany Kaul

UC Davis
Holly Ly
Annica Stull-Lane

UC Irvine
Kathleen Carlos
Haytham Effarah
Sangwoo Han
May Hui
Heechul Jun
Raji Nagalla
Yueqi Ren
Brian Tran
Katherine Yanes

UC San Diego
Andrea Dickey
Katherine Lee
Eulanca Liu
Kevin Tenerelli

UC San Francisco
Vikas Daggubati
Amrik Kang
Matthew Ryan
Alice Tang
Tina Zheng

UNC Chapel Hill
Cameron Adams
Danielle Brathwaite
Sherry Chao
Nate Diehl
Robert Hinson
Alison Mercer-Smith
Nicole Ochandarena
Meryem Ok
Kelly Olsen
Rani Richardson
Rebecca Rubinstein

University of Alabama at Birmingham
Samuel Chang
Jacob Files
Blake Frey
Sam Gary
Ashleigh Irwin
Shreya Kashyap
Benjamin Lin
Cristina Meehan
Robert Rosencrans
Garrett Wilson

University of Arizona, Phoenix
Ashley Guest

University of Arkansas
Lauren Morehead

University of Chicago
Saara-Anne Azizi
Meytal Chernoff
Sylvia Edoigiawerie
Mary Frith
P. Cody He
Anthony Hung
Maya Lozinski
Allen Zhu

University of Cincinnati
Courtney Giannini
Alison Jarmas
Brian Upton

University of Colorado
Christopher Alderman
Rachel Ancar
Hans Anderson
Eric Barrientos
Jessica Beynor
Chloe Briney
Amelia Burch
Meagan Chriswell
Rachel Cohen
Laurel Darragh
Keith Dodd
Nk Egbukichi
Mostafa El-Kalliny
Erin Fish
Marlie Fisher
Thomas Forman
Stefano Ginocchio
Annika Gustafson
Jordan Hickman
Brandon Hilliard
Joseph Hsieh
Connor Hughes
Anagha Inguva
Austin Jolly
Uma Kantheti
Amita Kashyap
Meghan Kellett
Shanawaj Khair
Kelsey Kines
Emily King
Bruce Kirkpatrick
Frances Li
Brian Lloyd
Hei-Yong Lo
Carley Miller
Daniel Moskop
Lily Nguyen
Raquel Ortega
Harry Park
Humphrey Petersen-Jones
Juan Santiago-Moreno
Brenda Seymour
William Sheeran
Soraya Shehata
Nathaniel Skillin
Ashlyn Stahly
Jackson Stocking
Andy Tekriwal
Jacqueline Turner
Taylor Yamauchi
Sarah Zych

University of Colorado/Cambridge
Kumar Thurimella

University of Connecticut
Alexandra Goetjen

University of Florida
Miles Cameron
Leanne Dumeny
Adam Grippin
Yuxing Xia

University of Iowa
Laura Marquez Loza
Shakoora Sabree
Akshaya Warrier
Kristin Weeks

University of Kansas
Carolyn Kaufman

University of Louisville
Mark Kravitz
Evan Tracy
Cassandra Woolley

University of Maryland
Alex Casella
Oleg Makarevich
Vishnu Rao
Olivia Uddin

University of Miami
Brett Colbert
Brandon Rosen

University of Minnesota
Kevin Lin

University of Mississippi
Hannah Turbeville
Jamarius Waller

University of Nebraska
Nozima Aripova
Safwan Elkhatib
Maranda Thompson

University of Rochester
Hayley Chang
Alan Finkelstein
Karl Foley
Ranran French
Gary Ge
Adwiteeya Misra
Duy Nguyen
Gavin Piester
Emily Przysinda
Shuyang Qin
Keshov Sharma
Jesse Wang

University of South Dakota Sanford
Ruthellen Anderson
Alexander Verma

University of Texas Medical Branch
James Fisher
Grayson Jackson
Jerricho Tipo

UT Houston
Carolina Garcia Garcia

UT San Antonio
Dene Betz
Trong Phat Do
Francisco Neal
Erica Osta
Anne Wells

University of Utah
James Carrington
Kendra Klag
Jason Kunisaki
Hayley Reynolds
Jenna Weber

University of Virginia
Ashley Bolte
HeeJin Cheon
Russell Hawes
Amanda Ward
Briana Wilson

University of Nevada, Reno
Majid Khan

Virginia Commonwealth University
Graeme Murray
Anuj Tharakan
Kyle Woisard

Washington University in St. Louis
Manasi Malik
Jaclyn Wright
Renee Wu

West Virginia University
Vincenzo Pizzuti

Yale University
Ryan Chow
Andin Fosam
Alanna Kaplan
Dan Li
Jovan Lopez
Lorenzo Sewanan
Anush Swaminathan

University of Cambridge/NIH
Yasemin Cole

University of British Columbia (Canada)
Daniel Kwon

Weizmann Institute (Israel)
Sharon Kagan Ben Tikva

Registration Information

Register @ https://mdphdnationalconference.regfox.com/35th-annual-mdphd-student-conference

Deadlines:

Abstract Submission Deadline***** (for Oral Presentations):
August 7, 2020

Oral Presentation Selection Announcement:
August 25, 2020

Early Registration (for complimentary conference water bottle, DoorDash coupons, and consideration for Poster presentations)
September 1, 2020

Cancellation with Refund:
September 10, 2020

*****Abstracts will be reviewed as application for oral presentation & diversity award.
******Dates may be subject to change

Registration Cost:

$150

Contact Information

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