4th Annual GCC Future of Immunology Symposium

April 9-10, 2024

Houston, Texas

Gulf Coast Consortia

QUANTITATIVE BIOMEDICAL SCIENCES

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The Gulf Coast Consortia (GCC), located in Houston, Texas, is a dynamic, multi-institution collaboration of basic and translational scientists, researchers, clinicians, and students in the quantitative biomedical sciences who benefit from joint training programs, topic-focused research consortia, shared facilities and equipment, and exchange of scientific knowledge. Working together, GCC member institutions provide a cutting-edge collaborative training environment and research infrastructure beyond the capability of any single institution. GCC research consortia gather interested faculty around research foci within the quantitative biomedical sciences and currently include Immunology, Antimicrobial Resistance, Cellular and Molecular Biophysics, Innovative Drug Discovery and Development, Integrative Development, Regeneration, and Repair, Mental Health Research, Single Cell Omics, and Translational Pain Research. GCC training programs focus on Biomedical Informatics, Computational Cancer Biology, Molecular Biophysics, Pharmacological Sciences, Precision Environmental Health Sciences, and Antimicrobial Resistance. Current members include Baylor College of Medicine, Rice University, University of Houston, The University of Texas Health Science Center at Houston, The University of Texas Medical Branch at Galveston, The University of Texas M. D. Anderson Cancer Center, Institute of Biosciences and Technology of Texas A&M Health Science Center and Houston Methodist Research Institute.

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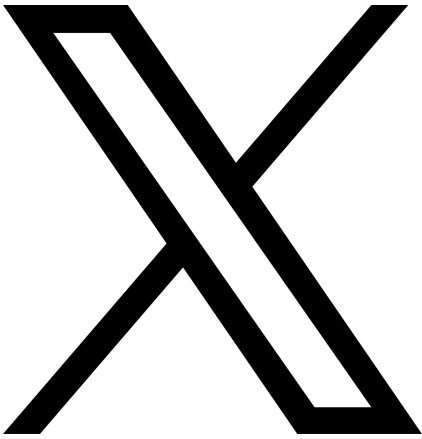**Yubin Zhou**, IBT TAMU

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Agenda

April 9-10, 2024

<u>**Day 1**</u>

1:30-2:00   Registration and poster set-up

2:00-2:05   Welcome
              Autumn Marsden, **PhD,** Gulf Coast Consortia
              David Corry, **MD,** Baylor College of Medicine

2:05-2:50   Keynote Presentation
              Engineered Regulatory T Cells for Tolerance Induction
              Megan Levings, PhD
              Univ. of British Columbia

Session 1
Convenor: **Weiyi Peng, MD, PhD,** Univ. of Houston

2:50-3:10   *Exploration of a Novel Oncolytic Virus as a Unique Platform for Harnessing*
               Cancer Immunotherapy
              Shaun Zhang, MD, PhD
              Univ. of Houston

3:10-3:30   *Structural Modeling and Dynamic Contact Analysis of TCRpHLA Complexes*
              Dinler Antunes, DSc
              Univ. of Houston

3:30-3:45   *T-Cell Dysfunction Associated with the LRRK2 Mutation in the Pathogenesis of*
               Parkinson's Disease
              Ningbo Zheng, PhD
              Univ. of Houston

3:45-4:15   Lightning poster talks- odd-numbered posters
              Mohanad Albayyaa, UT Medical Branch Galveston, Poster 13
              Sharon Bright Amanya, Baylor College of Medicine, Poster 15
              Pamella Borges, Univ. of Houston, Poster 17
              Jennifer Clinton, Baylor College of Medicine, Poster 19
              Kshiti Dholakia, Baylor College of Medicine, Poster 21
              Emily Henrich, Rice Univ., Poster 23
              Wenting Lu, Houston Methodist Research Institute, Poster 25
              Deblina Raychaudhuri, MD Anderson Cancer Center, Poster 27
              Alex Smith, Baylor College of Medicine, Poster 29
              Deepika Subramanyam, Baylor College of Medicine, Poster 31
              Yifan Wu, Baylor College of Medicine, Poster 33
              Dawei Zou, Houston Methodist Research Institute, Poster 35

4:15-5:15   Poster session odd-numbered posters (event hall)

Agenda

April 10, 2024

Day 2

8:30	Welcome **David Corry**, **MD,** Baylor College of Medicine
Convenor:	**Roza Nurieva, PhD,** MD Anderson Cancer Center
8:35-9:20	Keynote Presentation *Exploiting Antigen Presentation Pathways for Precision Immune Engineering* **Novalia Pishesha, PhD** Boston Children's Hospital
Session 2 **Convenors:**	**Univ. of Texas Medical Branch Galveston** **Alison Coady,** Univ. of Texas Medical Branch Galveston
9:20-9:40	*Role of IL-17 Pathways in Immunity and Immune Pathogenesis in TB and TB/HIV Co-infection* **Janice Endsley, PhD** Univ. of Texas Medical Branch Galveston
9:40-10:00	*Broad Protection and Host Immunity of mRNA Vaccines Against SARS-CoV-2 Variants* **Haitao Hu, PhD** Univ. of Texas Medical Branch Galveston
10:00-10:15	*A Complex Role of IFN-I on Antibacterial Immunity During Influenza A Virus and Streptococcus pneumoniae Co-pathogenesis* **Sunil Palani, MS** Univ. of Texas Medical Branch Galveston
10:15-10:30	Break
Session 3 **Convenors:**	**MD Anderson Cancer Center** **Roza Nurieva, PhD,** MD Anderson Cancer Center **Mauro Di Pilato, PhD,** MD Anderson Cancer Center
10:30-10:50	*The Epigenetic Regulation of T Cell-Mediated Anti-Tumor Immunity* **Sangeeta Goswami, MD, PhD** MD Anderson Cancer Center
10:50-11:10	*Welcome to the 4th Dimension: Tracking Leukocyte Migration in Homeostasis and Inflammation* **Jason M. Schenkel, MD, PhD** MD Anderson Cancer Center
11:10-11:25	*Immune Checkpoint Inhibitor-Mediated Colitis: Mechanistic Insights and Therapeutic Targets*

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Naimah Turner, MS
MD Anderson Cancer Center

11:25-11:55   Lightning talks-even number posters

Greyson Biegert, Baylor College of Medicine, Poster 16
Si Chen, Univ. of Houston, Poster 18
Jocelynn Colunga-Minutti, MD Anderson Cancer Center/Univ. of Texas Health, Poster 20
Casey Gonzales, Univ. of Texas Medical Branch, Poster 22
Zhouyihan Li, MD Anderson Cancer Center, Poster 24
Mansi Narula, Baylor College of Medicine, Poster 26
Suruchi Salgar, Baylor College of Medicine, Poster 28
Bin Brenda Su, Baylor College of Medicine, Poster 30
Ying Wang, Baylor College of Medicine, Poster 32
Haonan Zhouyao, Baylor College of Medicine, Poster 34

11:55-12:30   lunch (event hall)
12:30-1:30   posters-even number posters

Session 4   **Baylor College of Medicine**
Convenors: **David Corry, MD,** Baylor College of Medicine
                 Sharon Amanya, Baylor College of Medicine

1:30-1:50   *Cell-Based Therapeutic Vaccination as Adjuvant Therapy for Glioblastoma: Ongoing Phase I Analysis*
               William Decker, PhD
               Baylor College of Medicine

1:50-2:10   *Dietary Lipid Effects on Intestinal Macrophage Antimicrobial Responses to Intestinal Injury*
               Andrea McAlester, PhD
               Baylor College of Medicine

2:10-2:25   *Let-7 MicroRNA Maintains Lung Epithelial Stem Cell Homeostasis via EZH2 Histone Methylation*
               Matthew Seasock, BS
               Baylor College of Medicine

2:25-2:40   Break

Session 5   **UT Health Science Center/Rice University/ Houston Methodist Hospital**
Convenors: **Jin Wang, PhD,** Methodist Hospital Houston
                 Max Mamonkin, PhD, Baylor College of Medicine

2:40-3:00   *Bone Marrow Mononuclear Cell Therapy Improves Traumatic Brain Injury Via IDO-Expressing Monocytes*
               Joana Bianchi, PhD
               University of Texas Health Sciences Center

Agenda

3:00-3:20   *Use of Biodegradable Pulsatile Release Microparticles to Enable Single-Injection Vaccination for Rabies Post-exposure Prophylaxis*
Tyler P. Graf, MSc
Rice Univ.

3:20-3:35   *A Th1 Cytokine Response Is Associated with Protection from Candida Gut Colonization in Critically Ill Patients*
Max Adelman, MD, MSc
Houston Methodist Research Institute and Weill Cornell Medical College

3:35   Closing remarks and award

Max Adelman, MD, MSc
Assistant Professor of Medicine, Academic Institute
Assistant Clinical Member, Research Institute
Houston Methodist
Weill Cornell Medical College
A Th1 Cytokine Response Is Associated with Protection from Candida Gut Colonization in Critically Ill Patients

Dr. Adelman clinician-scientist who practices Infectious Diseases and Critical Care Medicine Houston Methodist Hospital. He completed internal medicine residency at Massachusetts general hospital followed by fellowship training in Infectious Diseases and Critical Care and Emory University. His research focuses on improving outcomes for critically ill patients with, or at risk of, severe infections. He has a particular interest in multidrug resistant Candida infections, including the impact of immune dysregulation during critical illness on candida colonization and infection.

Dinler A. Antunes, DSc
Assistant Professor in Computational Biology
Biology and Biochemistry
University of Houston
Structural Modeling and Dynamic Contact Analysis of TCRpHLA Complexes

Dinler is a computational biologist interested in Biomedical applications, including cancer immunotherapy, antiviral vaccine development, and drug discovery. He has a background in immunology and virology, and is currently an Associate Professor in Computational Biology at the Department of Biology and Biochemistry at the University of Houston. His research focuses on developing structural bioinformatics methods that can be used to improve the selection of peptide-targets and T-cell receptors with potential therapeutic use for personalized cancer immunotherapy, as well as the computational assessment of potential risks associated with off-target toxicity induced by these therapies. He is also broadly interested in problems related to protein ligand modeling and simulation, especially in which regards to peptide and peptidomimetic inhibitors. Dr. Antunes is also a former Keck postdoctoral fellow of the Computational Cancer Biology Training Program (CCBTP). More at dinlerantunes.com.

Joana Bianchi, PhD
Postdoc
University of Texas Health Science Center Houston
*Bone Marrow Mononuclear Cell Therapy Improves
Traumatic Brain Injury Via IDO-Expressing Monocytes*

Joana graduated with an MSc in Biomedical Engineering from Universidade do Porto in 2013. She went on to finish her PhD in Immunology at Universidade de Lisboa in 2019, where she studied the expansion and characterization of donor-specific regulatory T cells, envisaging their clinical translation to use in graft versus host disease prevention. Her current work at UTHealth Science Center focuses on finding strategies for the treatment of traumatic brain by targeting immune cells causing neuroinflammation.

William K. Decker, PhD
Professor
Pathology and Immunology
Baylor College of Medicine
Cell-Based Therapeutic Vaccination as Adjuvant Therapy for Glioblastoma: Ongoing Phase I Analysis

Dr. William Decker is a Professor in the Department of Pathology & Immunology at Baylor College of Medicine. Dr. Decker received a B.S. in Biology from Tufts University and a Ph.D. in Molecular in Human Genetics from Baylor College of Medicine in 2001. Following early career work in industry, he spent seven years as Senior Research Scientist in the Department of Stem Cell Transplantation and Cellular Therapy at the University of Texas M.D. Anderson Cancer Center where he studied basic dendritic cell biology, transplant immunology, and developed cell-based treatment strategies for cancer. In 2011, Dr. Decker joined the faculty at Baylor College of Medicine, establishing a research group that studies basic dendritic cell immunobiology and maintains basic, translational, and clinical immunotherapy research programs for a variety of different cancers. He holds multiple federal R01 grants to study basic mechanisms of dendritic cell immune governance and previously served as a permanent member of the III NIH R01 study section. He is a sponsor or investigator on three INDs, an inventor on nine patents, and serves on the scientific and medical advisory boards of Diakonos Oncology, a clinical stage immuno-oncology company.

Janice Endsley, PhD
Professor
Microbiology and Immunology
University of Texas Medical Branch
Role of IL-17 Pathways in Immunity and Immune Pathogenesis in TB and TB/HIV Co-infection

Janice Endsley (PhD) is a Professor in the Department of Microbiology and Immunology, and Associate Dean for Student Affairs in that Graduate School of Biomedical Sciences, at the University of Texas Medical Branch in Galveston, Texas, USA. She is an Immunologist whose research focuses on immunity to Tuberculosis (TB) related to vaccine development and human immunodeficiency virus (HIV) co-infection. Her laboratory developed the humanized mouse model of TB and HIV co-infection, and utilizes this model for basic and translational research. Through collaboration with scientists at the Kenya Medical Research Institute, she further studies immune disturbances in human subjects with TB and HIV co-infections.   Her laboratory provides training for undergraduate, medical, pre-doctoral, and postdoctoral trainees in multiple infectious disease training programs.

Sangeeta Goswami, MD, PhD
Physician Scientist
Genitourinary Medical Oncology, Immunology
MD Anderson Cancer Center
The Epigenetic Regulation of T Cell-Mediated Anti-Tumor Immunity

Dr. Sangeeta Goswami is a physician-scientist in the Department of Genitourinary Medical Oncology, Department of Immunology, Division of Cancer Medicine, and the James P. Allison Institute at The University of Texas MD Anderson Cancer Center, Houston, Texas, USA. She obtained her medical degree from the Gauhati Medical College in • DrAssam, India, and PhD in Immunology from Baylor College of Medicine in Houston, Texas, USA. She completed her Internal Medicine Residency from the University of Pittsburgh Medical Center (UPMC) in Pittsburgh, PA, and Medical Oncology Fellowship from The University of Texas MD Anderson Cancer Center, Houston, Texas, USA.

Dr. Goswami has published numerous original research articles and reviews in high-impact journals such as Nature Medicine, Nature Immunology, Science, Nature Reviews Immunology, and Science Translational Medicine which enabled development of novel combination immunotherapy to treat cancer patients.

Dr. Goswami's clinic is focused on treating patients with renal cell carcinoma and urothelial carcinoma. Dr. Goswami's laboratory in the Department of Immunology focuses on understanding the cellular state and plasticity of the tumor-immune ecosystem and its role in determining response to immune checkpoint therapy. Dr. Goswami has designed multiple investigator-initiated clinical trials based on her pre-clinical data and currently leading them as a principal investigator.

Recently, Dr. Goswami was elected to be a part of the "Extended Leadership Team" for the Break Through Cancer (BTC) Glioblastoma (GBM) team, a research alliance between The University of Texas MD Anderson Cancer Center, Dana Farber Cancer Institute, Massachusetts Institute of Technology, Johns Hopkins University, and Memorial Sloan Kettering Cancer Center. As a part of this multi-disciplinary alliance, Dr. Goswami will lead the discovery science work delineating myeloid cell biology to explore therapeutic avenues in GBM. Dr. Goswami received numerous awards, including the Andrew Sabin Award in 2021 for high-risk-high impact research for emerging leaders.
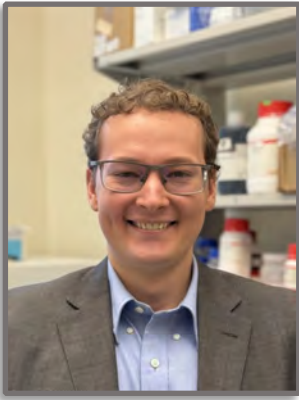
Tyler Graf, MSc
Graduate Student
Rice University
Use of Biodegradable Pulsatile Release Microparticles to Enable Single-Injection Vaccination for Rabies Post-exposure Prophylaxis

Tyler Graf is a 5th-year PhD bioengineering student at Rice University. His interest is exploring biomaterials to temporally control the release of vaccine to enable a strategy for single-injection vaccinations. He obtained my bachelor's and master's degrees in biomedical engineering at Rensselaer Polytechnic Institute.

Haitao Hu, PhD
Associate Professor
Microbiology and Immunology
University of Texas Medical Branch
Broad Protection and Host Immunity of mRNA Vaccines
Against SARS-CoV-2 Variants

Dr. Hu is a viral immunologist and an associate professor of Microbiology and Immunology at UTMB. He did his PhD training with the Nobel Laureate Dr. Drew Weissman at the University of Pennsylvania, followed by a postdoc training at the US Military HIV research Program of Water Reed Army Institute of Research. He joined UTMB as an assistant professor in 2015 and was promoted to associate professor in 2021. Research in his laboratory investigates viral pathogenesis & host immunity (focusing on HIV/AIDS) and employs RNA platform to develop novel vaccines and therapeutics. In response to the COVID-19 pandemic, he and his collaborators have developed an mRNA vaccine that provides broad protection against emerging SARS-CoV-2 variants as a promising pan-COVID-19 vaccine candidate.

Megan K. Levings, PhD
Professor, Department of Surgery and School of
Biomedical Engineering, University of British Columbia
Canada Research Chair in Engineered Immune
Tolerance
Lead, Childhood Diseases Theme, BC Children's
Hospital Research Institute

Dr. Megan Levings is a Professor in the Department of Surgery and School of Biomedical Engineering at the University of British Columbia and BC Children's Hospital Research Institute. Her lab studies how a special kind of white blood cell, known as a T regulatory cell, could be used as a cellular therapy to stop harmful immune responses. She is internationally recognized in the field of human immunology and leads a vibrant group of trainees and staff who are researching how to use T regulatory cells to replace conventional immunosuppression in the context of transplantation and autoimmunity. She has won numerous awards, including 2020 YWCA Woman of Distinction, Science, Research & Technology, 2022 Simon Fraser University Outstanding Alumni award, and 2022 UBC Faculty of Medicine Distinguished Researcher in the Basic/Foundational Science Category.

Keynote presenter

Andrea McAlester, PhD
Instructor
Pathology and Immunology
Baylor College of Medicine
Dietary Lipid Effects on Intestinal Macrophage Antimicrobial Responses to Intestinal Injury

Dr. Andrea McAlester is an early career faculty in the Department of Pathology and Immunology.

The research in her lab focuses on understanding dietary lipid effects on intestinal immune function and the influence on intestinal disease development. Dr. McAlester's research seeks to develop diet interventions that support reparative immune functions to reverse tissue-damaging conditions in intestinal diseases, such as inflammatory bowel disease. Her interest in biomedical research began during her undergraduate studies at Clark Atlanta University, where she received her B.S. in Biology. Dr. McAlester received her Ph.D. in Molecular Physiology and Biophysics from Vanderbilt University, where her studies focused on immunometabolism. She then joined Baylor College of Medicine as a postdoc in the Center for Metagenomics and Microbiome Research, where she studied the impact of microbial signals and high-fat diet feeding on intestinal immune tissue repair functions. These studies set the foundation for Dr. McAlester's K01 award from the NIDDK in 2020 and the lab's current research focus.

Sunil Palani, MS
Graduate Student
University of Texas Medical Branch
A Complex Role of IFN-I on Antibacterial Immunity During Influenza A Virus and Streptococcus pneumoniae Co-pathogenesis

Sunil Palani is a 5th-year Ph.D. student in the M&I program at UTMB. He graduated with a Bachelor of Engineering in Biotechnology in 2014 from M S Ramaiah Institute of Technology, India. His love for immunology and microbiology led him to pursue his master's degree in medical biotechnology from the University of Illinois at Chicago, where he studied the cellular mechanisms in B-1 cells in response to an immunization strategy termed "suppressed immunization" using dexamethasone as an adjuvant as a therapeutic strategy to treat autoimmune diseases. He enjoyed being on the bench and doing research. Shortly after graduation, he moved to Boston and briefly worked for a biotech company before moving to Takeda Vaccines Inc. His team and he worked on the Dengue vaccine candidate, TAK003, at Takeda. He performed an RVP-based serotype-specific neutralization assay for sera samples from the Phase II clinical trial to determine the TAK003's serum potency, antibody titer, and efficacy. The whole experience was rewarding.

Coming from a family of teachers, he has an innate interest in sharing and imparting the knowledge he loves and enjoys. Combined with his deep love for research, he started his Ph.D. in 2019 under the guidance of Dr. Keer Sun. For his Ph.D. thesis, he is investigating the role of Alveolar macrophages in pulmonary infections and the synergistic effect of Type I and Type II IFNs on antibacterial immunity during influenza-induced pneumococcal pneumonia. His journey so far has been a rollercoaster; that being said, it's his journey, and he wouldn't trade it for anything else. UTMB is a fantastic school to study immunology and infectious diseases. He is passionate about immunology, microbiology, infectious diseases, global health, and nutrition.

Novalia (Nova) Pishesha, PhD
Assistant Professor
Immunology
Boston Children's Hospital
Exploiting Antigen Presentation Pathways for Precision Immune Engineering

Novalia (Nova) Pishesha earned her PhD in Biological Engineering from MIT in 2018, where her research focused on the engineering of red blood cells for the treatment of autoimmune diseases, hyperlipidemia, and the development of biodefense strategies against lethal bioweapons. Following her graduation, Nova was elected a Junior Fellow at the Harvard Society of Fellows and continued her research in the laboratories of Professors Hidde Ploegh and Sangeeta Bhatia at the Boston Children's Hospital and the Koch Institute, respectively. Her work has since revolved around alpaca-derived single domain antibody fragment (nanobody)-based platform to create novel therapeutics for immune modulation, specifically for treating various autoimmune diseases and enhancing vaccine efficacy. In 2022, she co-founded a biotech company, Cerberus Therapeutics, based on this technology.

Nova has been recognized as one of the 2021 MIT Technology Review Innovators Under 35 for the Asia Pacific region and was listed in The Boston Globe's STAT+ Wunderkinds. She is also a recipient of the National Multiple Sclerosis Foundation Career Transition Award. In January 2024, Nova initiated her own laboratory at the Boston Children's Hospital and Harvard Medical School, where she serves as an Assistant Professor in the Division of Immunology. Her lab is dedicated to advancing the understanding and application of immune engineering to combat pathogenic immunity.

Keynote presenter

Jason M. Schenkel, MD, PhD
Assistant Professor
Translational Molecular Pathology, Immunology
Department of Laboratory Medicine
MD Anderson Cancer Center
Welcome to the 4th Dimension: Tracking Leukocyte Migration in Homeostasis and Inflammation

Dr. Schenkel is a basic cellular immunologist who is currently an Assistant Professor in the Department of Translational Molecular Pathology, Department of Immunology, and the Department of Laboratory Medicine. He completed his M.D./Ph.D. at the University of Minnesota from 2009-2016. Dr. Schenkel performed his dissertation work in Dr. David Masopust's Lab where he interrogated the ontogeny, distribution, and function of tissue resident memory CD8+ T cells in mice after acute viral infection. He then completed his clinical residency in clinical pathology at Brigham and Women's Hospital, his clinical fellowship in transfusion medicine at Harvard Medical School, and a post-doctoral fellowship at MIT in the laboratory of Dr. Tyler Jacks. At MIT, Dr. Schenkel's work focused on understanding how CD8+ T cells in the tumor draining lymph node are a critical functional reservoir that can continually seed the tumor microenvironment. Moreover, he found that type I conventional dendritic cells were critical for continuously stimulating CD8+ T cells in the tumor draining lymph node. Dr. Schenkel started his laboratory at MD Anderson in 2022. The Schenkel Lab is focused on understanding how tumor and tissue microenvironments engage with immune cells locally and systemically to either drive or inhibit the immune response to cancer.

Matthew Seasock, BS
PhD Candidate, Rodriguez Lab
Immunology & Microbiology Graduate Program
Clinical Translational Research Program
Baylor College of Medicine

Let-7 MicroRNA Maintains Lung Epithelial Stem Cell Homeostasis via EZH2 Histone Methylation

Matthew Seasock received his Bachelor of Science in Cell & Molecular Neuroscience at Temple University. His undergraduate research focused on traumatic brain injuries, and he published a method for engineering an in vitro blood-brain barrier using a microfluidic chip for neuropharmacology and neuroimmunology studies. Matthew then worked as a technician in a genetics lab studying diabetic kidney disease at the University of Pennsylvania Perelman School of Medicine where he published several articles. Now, Matthew is a 5th year graduate student in the Immunology & Microbiology Program at Baylor College of Medicine in Dr. Antony Rodriguez's lab where he studies how microRNAs regulate alveolar stem cell fate and pulmonary fibrosis.

Naimah Turner, MSc
Research Assistant
MD Anderson Cancer Center
Immune Checkpoint Inhibitor-Mediated Colitis: Mechanistic Insights and Therapeutic Targets

Naimah Turner graduated with a B.A in Biology from Washington University in St. Louis in 2019 followed by a M.S in Medical Physiology from Case Western Reserve University School of Medicine. She is currently a Research Assistant in Dr. Roza Nurieva's laboratory in the Immunology Department at MD Anderson Cancer Center. Her current research aims to establish a preclinical murine model of immune checkpoint therapy-induced colitis that will allow for the identification of mechanisms underlying pathogenesis and potential therapeutic targets. Additionally, she investigates the links between the microbiome and tumor immune microenvironment that reflects outcomes in tumor progression.

Shaun Xiaoliu Zhang, MD, PhD
Professor
Biology and Biochemistry
Director, Center for Nuclear Receptors and Cell Signaling
College of Natural Sciences and Mathematics
Oncolytic Viral Therapy in Combination with Immunotherapy

Dr. Shaun Zhang earned his doctoral degree from the John Curtin School of Medical Research at Australian National University. After postdoc training at Adelaide, Australia, and Cambridge, UK, he joined Baylor College of Medicine as a faculty member. He worked there for ten years before transitioning to the University of Houston, where he currently serves as a tenured professor and holds the M.D. Anderson endowed professorship. Furthermore, he has taken on the role of Director of the Center for Nuclear Receptors and Cell Signaling at the University of Houston. Dr. Zhang's research focuses on cancer virotherapy and immunotherapy, with a sustained interest in finding a way of synergistically combining these two promising therapeutic principles to maximize the therapeutic benefit against solid tumors. His ultimate goal is to translate the research outcome from his lab into clinical application.

Ningbo Zheng, PhD
Postdoc
University of Houston
T-Cell Dysfunction Associated With The LRRK2 Mutation In The Pathogenesis Of Parkinson's Disease

Ningbo Zheng, received her PhD at Tianjin Medical University, Tianjin, China. In Jan 2020, she started her postdoctoral fellowship, concentrating on T cell immunotherapy against tumors, including using CAR-T and a new tumor-specific Th9 cell-paradigm to eradicate advanced tumors. She joined Dr. Peng's lab in Feb 2022, working on the LRRK2-mediated T cell dysfunction in Parkinson's disease (PD) project, Specifically, she aims to determine whether the LRRK2 G2019S mutation contributes to the pathogenesis of PD by influencing T cell functionality.

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Androgen Deprivation Therapy and the Risk of Rheumatic Autoimmune Diseases in Men with Prostate Cancer

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Prostate cancer is the second most common cause of cancer death among men. Most men with prostate cancer are diagnosed at localized stages and treated with standard options including radiation, hormonal therapy, or surgery. Androgen Deprivation Therapy (ADT) is one of the mainstay treatments for prostate cancer patients, but it carries a range of possible adverse effects, including cardiovascular and autoimmune diseases. The mechanistic and biological pathways of androgens in regulating the immune cells and the physiological balance of autoimmunity are altered through ADT by increasing the number of regulatory T-cells, cytokines, and pro-inflammatory markers. Rheumatic autoimmune diseases (RAD) include rheumatoid arthritis, lupus, ankylosing spondylitis, and Sjogren's syndrome. Objective: To examine whether ADT increases the risk of RAD in men with prostate cancer.

Methods: A cohort of patients aged >=66 years who were first diagnosed with stages (Ⅰ-Ⅲ) prostate cancer between 2010 – 2019 was identified, using the Texas Cancer Registry linked to Medicare data. The exposure to ADT was defined by the receipt of a GnRH agonist/antagonist, or orchiectomy. All patients were followed until the *diagnosis of RAD* or censored by the end of the study follow-up period or death. The patients with non-ADT were matched (1:1) to those with ADT exposure. The Kaplan-Meier method was used to produce unadjusted estimates of survival free of any RAD among the groups that did or did not receive ADT. The Cox proportional hazard analyses were used to estimate hazard ratios (HRs) with 95% CI of RAD associated with the two groups. Both models were adjusted for potential confounders in the cohort as age, race, education, marital status, poverty, metro residence, grade, stage, comorbidity index, and concomitant medications.

Results: A total of 10,100 matched patients were included in the analysis. The failure rates of RAD over time calculated using the Kaplan-Meier curves showed that patients receiving ADT had higher rates of RAD of 11%(95% CI: 0.10 - 0.12), while men who received non-ADT had lower rates of RAD of 9%(95% CI: 0.08 - 0.10). In the Cox proportional regression model, ADT use was significantly associated with an increased risk of RAD, HR = 1.29(95% CI: 1.17-1.56).

Poster 13
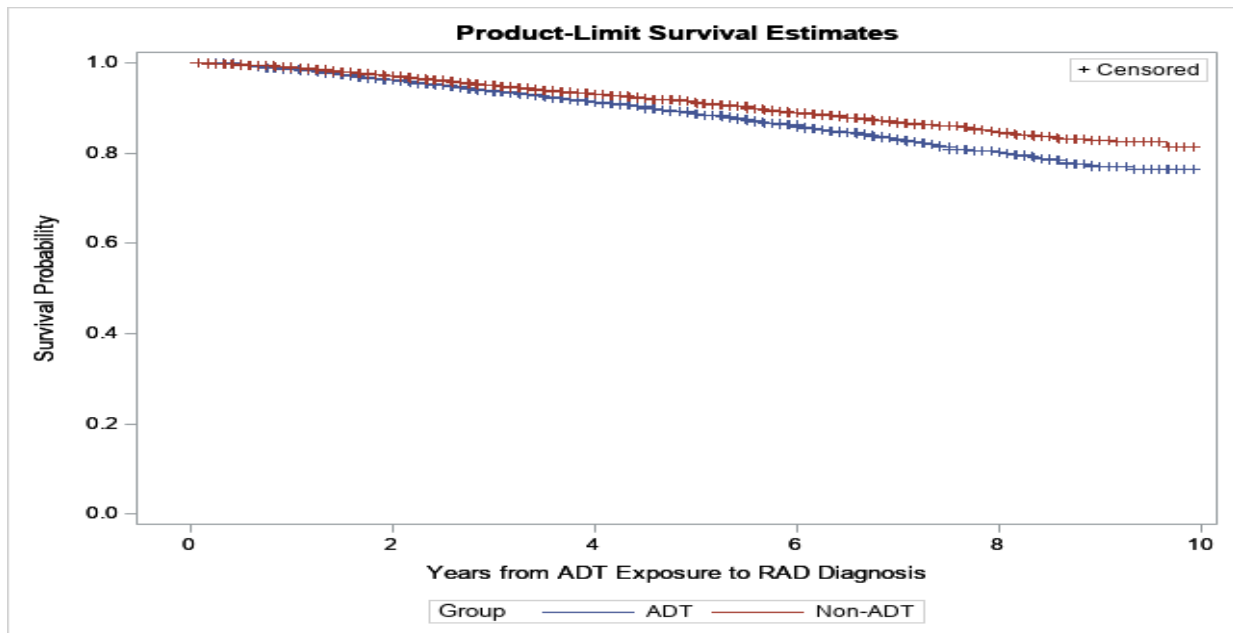
Figure 1: Kaplan-Meier shows the survival probability of free RAD

Conclusion: Our analyses showed that patients who received ADT had a 29% increased risk of being diagnosed with RAD. Linking ADT to an increased risk of RAD adds to the broad list of known adverse effects, which have a significant clinical and public health impact. Our investigation is consistent with two large population-based studies both of which showed an increased risk of RAD in prostate cancer patients who received ADT. Hence, it is imperative for clinicians to assess the care patterns and engage in discussions regarding potential adverse effects prior to initiating ADT.

Multi-aminoacyl tRNA Synthetase Complex-mediated Sensing of Antigen Homology Dictates mTORC1-dependent T_H1 Polarization in Dendritic Cells

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Dendritic cells (DCs) initiate, direct and regulate Type 1 helper (T_H1) responses that are critical for antitumor immunity but remain under exploited largely because the mechanisms are not well understood. We have previously described a novel strategy for T_H1 polarization of DCs in which the homology of antigenic epitopes plays a critical role. When bound MHC class I and II peptide epitopes share an identical stretch of at least 5 amino acids, this homology is sufficient to drive robust T_H1 polarization, rendering manipulation of this mechanism an attractive target for cancer immunotherapy. This study explores the mechanisms for antigen homology sensing and the downstream signaling pathways that mediate T_H1 polarization. Using mass spectrometry, we identified that MHC molecules interact with the multi-aminoacyl tRNA synthetase (mARS) complex, a multi-subunit protein complex comprised of aminoacyl tRNA synthetases (aaRS) and interacting proteins (AIMPs). Further, the composition of aaRS within the complex undergoes changes consistent with amino acids present in the homologous MHC peptides; suggesting a sensing role. Knockout of AIMP1, a critical scaffold of the mARS complex revealed the mechanistic target of rapamycin complex 1 (mTORC1) pathway as a significant downstream effector that's inhibited following homologous antigen loading. Accordingly, Co-IP showed a direct interaction of the mARS with Rags, small G proteins known to transmit signals from amino acid sensors to the mTORC1 complex. Consistent with the known regulation of *IL12*/*IL10* axis by mTORC1 via NFkB, ChIP PCR showed significantly high binding of NFκB to the *IL12* promoter and a reduction in *IL10* promoter binding in DCs loaded with homologous antigens. Additionally, IL-12 was significantly upregulated with concomitant reduction of IL-10. These findings describe the intricacies of a novel mechanism through which T_H1 polarization in DCs is governed by the homology of MHC peptide epitopes sensed by the mARS complex (Fig 1). Further delineation of this complex mechanism will be of paramount importance to the identification of specific, druggable targets, the manipulation of which will enhance therapeutic outcomes in cancer immunotherapy.
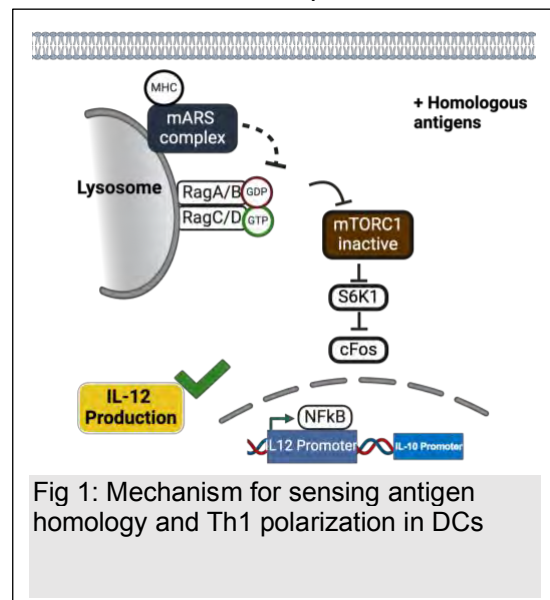
Fig 1: Mechanism for sensing antigen homology and Th1 polarization in DCs

"Off-The-Shelf" Combination CAdVEC and CAR-NK Cell Immunotherapy for Pancreatic Ductal Adenocarcinoma

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To thwart the dynamic challenges presented by solid tumors, our lab developed an oncolytic adenoviral platform (CAdVEC) designed to counteract immunosuppressive tumor microenvironments (TME), and simultaneously improve immune cell infiltration and anti-tumor activity of endogenous and adoptive CAR-modified immune cells.

Currently in clinical testing, CAd*Trio* (expressing IL-12p70, anti-PD-L1 minibody, and HSV-tk safety switch) reinforces adoptive CAR-T and endogenous natural killer (NK) cell activity in preclinical models, including pancreatic ductal adenocarcinoma (PDAC); a class of treatment resistant tumors characterized by poor immune cell infiltration and activity in the TME. Our clinical data demonstrates significant anti-tumor effects in local CAd*Trio*-treated tumors and has shown to be safe in combination with autologous CAR-T cells (NCT03740256). Despite this success, CAR-T cell products are costly, difficult to generate and of inconsistent quality.

To avoid these challenges, adoptive NK cell therapies have garnered increasing interest as a readily deployable "off-the-shelf" alternative. Based on our observations of improved NK cell function in response to CAd*Trio* transgene expression, we hypothesized that CAd*Trio* combined with adoptive CAR-NK cell therapy could provide sustained systemic tumor targeting as an "off-the-shelf" combination immunotherapy.

As a single agent therapy, CAR-NK cells have limited anti-tumor activity against PDAC in immunodeficient models. However, in the context of a tumor treated with CAd*Trio,* CAR-NK cell persistence at the tumor site is significantly increased, conferring improved tumor growth control and survival. RNAseq analysis indicates that the underlying mechanism involves CAd*Trio* transgene-dependent activation of memory-like NK cell development pathways. Since CAR-NK cells can utilize natural ligand/receptor interactions to eliminate cancer cells, we tested this combination immunotherapy in a heterogeneous PDAC PDX model. Mice receiving CAd*Trio* combined with CAR-NK cell therapy displayed significantly improved tumor growth control and survival compared to those receiving single agent treatment. Studies in humanized mice have indicated that "off-the-shelf" CAd*Trio* and CAR-NK cell combination therapy is a well-tolerated and significantly effective PDAC tumor growth control strategy. Further studies in humanized mice will elucidate the anti-tumor contributions of the endogenous immune system in the context of this combination immunotherapy.

Overall, our data indicates local CAd*Trio* and systemic CAR-NK cell combination immunotherapy may be an effective immunotherapy for treatment-resistant PDAC and potentially other immunologically deficient solid tumors.

Insights into Immune-Malignant Cell Interplay in Acute Myeloid Leukemia: Deciphering TCR Repertoire Dynamics and Therapeutic Implications

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Acute Myeloid Leukemia (AML) is characterized by the rapid proliferation of immature myeloid cells, posing a significant treatment challenge due to its resistance. Understanding the interplay between the immune system and malignant cells is crucial for optimizing cancer immunotherapy. Analyzing the T-cell receptor (TCR) repertoire provides valuable insights into this relationship. We analyzed single-cell TCR sequencing data from 6 healthy controls and 19 pre/post-treatment AML patients (50 samples) from 2 cohorts: eight relapsed/refractory (Rel/Ref) (22 samples) and eleven newly diagnosed (NewDx) (28 samples). Our analysis focused on the percentage of unique clonotypes across all samples and within each group to assess diversity. We also examined the relative abundance and clonal proportion to understand clonotype expansion. Results revealed a heterogeneous, unique clonotype distribution, with healthy samples exhibiting the highest diversity (Fig 1A and B). Health samples predominantly contained rare clonotypes, occupying over 75% of their space. Surprisingly, the NewlyDx_pre group exhibited a relative abundance pattern akin to RelRef_post, with less than 50% representing rare clonotypes. The NewlyDx_post group displayed the most rare abundance pattern, with the less amount of large clonotypes group between the samples (Fig 1C). Interestingly, we continue to see similar abundance patterns between NewlyDx_pre and RelRef_post samples in the varied occupancy of the top 10 clonotypes, with the NewlyDx_Post samples presenting the most diverse repertoire space occupancy (Fig 1D). These findings underscore the complex dynamics of TCR repertoire in AML progression and treatment response, providing valuable insights for therapeutic strategies.

Figure 1: Clonotype Diversity Analysis. A. Percentage of unique clonotypes measured across all 50 samples and 6 control samples. B. Percentage of unique clonotypes categorized by group. C. Relative abundance occupied by clones within each group. D. Clonal proportion based on clonal indices within each group. Groups include: Health (control samples), Newly Diagnosed (NewDx) pre and post-treatment, and Relapsed/Refractory (Rel/Ref) pre and post-treatment.
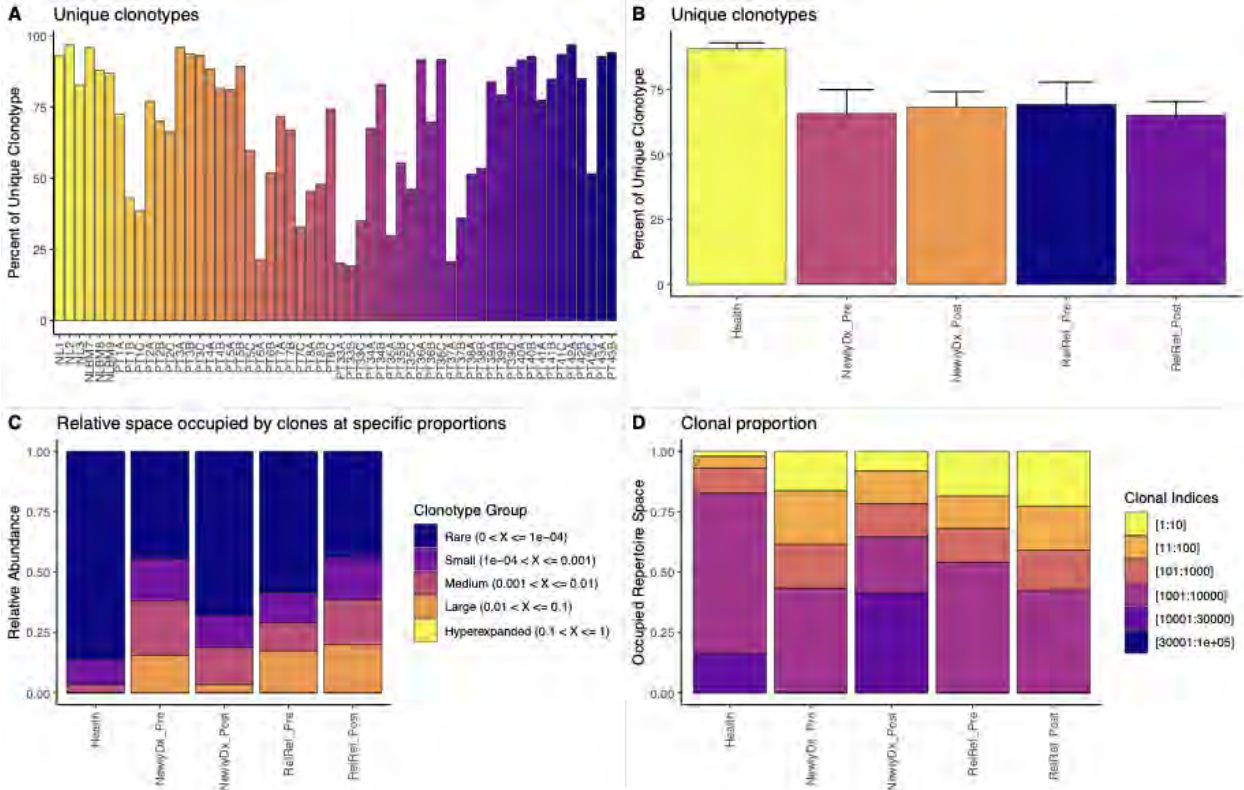
Role of CCR7^{+} Dendritic Cells in the Melanoma Tumors.

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Low immunogenic tumors are a big challenge in cancer immunotherapy since they do not respond to the current treatments. Many studies have focused on enhancing the activation and proliferation of T effector (Teff) cells and on preventing their exhaustion. Antigen-presenting cells, specifically dendritic cells (DCs), play a significant role in cancer rejection by promoting antigen-specific Teff responses. Among classical DCs, an activated subset that expresses CCR7 and Fascin-1 is conserved across humans and mice. CCR7^{+}DCs co-localize with intratumoral Teff cells and control their accumulation and survival in melanoma. Despite correlative evidence suggesting a role for CCR7^{+}DCs in promoting CD8 T cell functions and improved clinical outcomes, the mechanistic role of CCR7^{+}DCs in the TME is still unclear. Our goal is to combine the YUMM3.3 (Braf^{V600E}Cdkn2a$^{-/-}$) and YUMM1.7 (Braf^{V600E}Cdkn2a$^{-/-}$Pten$^{-/-}$) melanoma with innovative genetically engineered mouse models to mechanistically define the role of CCR7^{+}DCs in melanoma.

Our findings show that YUMM3.3 tumors grow significantly slower than YUMM1.7 tumors. Furthermore, the delayed growth of YUMM3.3 correlates with an enhanced infiltration of both CCR7^{+}DCs and cytotoxic antigen-specific CD8 T cells in comparison to YUMM1.7 tumors. To investigate this finding further, we developed a novel double knock-in mouse model (Zbtb46$^{Dre-RFP}$CCR7$^{STOProx/rox-cre-EGFP}$), where we could specifically deplete CCR7^{+}DCs by let them express diphtheria toxin (DTA). When Zbtb46$^{Dre-RFP}$CCR7$^{STOProx/rox-cre-EGFP}$ mice were crossed with ROSA-$^{STOPflox/flox}$ DTA mice, the number of CCR7^{+}DCs was reduced by 70% in the TME of YUMM3.3 tumors, and the tumor control was partially lost compared with CCR7^{+}DCs sufficient mice. 2/3 weeks after tumor implantation, the depletion of CCR7^{+}DC positively correlated with the intratuomoral infiltration of antigen-specific CD8 T cells and CD4 T cells. In addition to the depletion of CCR7^{+}DCs, we exploited a pharmacological approach based on the inhibition of Fascin-1 to increase the abundance of CCR7^{+}DCs in the YUMM3.3 melanoma tumors. We observed that the inhibition of Fascin-1 enhanced the retention on CCR7^{+}DCs in tumors and delayed the growth of YUMM3.3 tumors. In conclusion, our findings suggest a relevant role of CCR7^{+}DC in the control of the YUMM3.3 melanoma.

Deciphering Population Heterogeneity in Vaccine-induced Immunity: A Mechanistic Model for Immune Fingerprinting

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Vaccines are pivotal in combating infectious diseases, saving millions of lives worldwide and vastly improving public health. Despite their success, the effectiveness of vaccines varies across individuals, posing a significant challenge in achieving optimal community-wide immunity. Several host factors such as virus pre-exposure, age, sex, genetics, and co-morbidities can influence the strength of the vaccine-induced immune response. This variability thus affects the population-scale efficacy of vaccines and underlines the need for an approach to optimize the use of vaccines to improve outcomes.

To address this problem, we developed a mathematical model based on ordinary differential equations to study the immune response process. We explored extensive clinical data from literature involving immune response to COVID-19 vaccines in healthy adults (N = 1,593). Despite being healthy, these individuals exhibited significant variability in antibody response. We fitted our model to individual-scale immune response kinetics data (over 230 days) to estimate unknown model parameters. The model fits were in good agreement with the data (Pearson correlation R > 0.9); through global sensitivity analysis we identified production rate of antibodies per cell (P_{Ab}) and activation rate of plasma cells (T_P) as the top two parameters governing antibody response. Statistically significant differences were observed in the values of these two parameters between high and low responders, which were defined as subjects exhibiting high versus low area under the antibody kinetics curve, respectively. We thus infer that the difference in humoral response between individuals can be attributed to differences in their P_{Ab} and T_P values, suggesting that these parameters may constitute the broader immune signature shaping vaccine immunogenicity. These preliminary findings warrant further investigation, emphasizing the need for a more nuanced and quantitative characterization of immune response.

Our study introduces a new way to understand why vaccine responses vary and suggests a method to improve vaccine effectiveness for different groups of people. This could lead to better vaccine distribution, more efficient clinical trials, and, ultimately, personalized vaccination plans, making public health decisions more effective.

MTA-cooperative PRMT5 Inhibitors Enhance T cell-mediated Antitumor Activity in MTAP Loss Tumors

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9p21.3 is a chromosomal region that is naturally deleted in many cancer types. The cyclin-dependent kinase inhibitor 2A (*CDKN2A*) and methylthioadenosine phosphorylase (*MTAP*) are frequently lost as a result. This co-deletion leads to a decrease of tumor-infiltrating lymphocytes (TIL) of cancer patients. MTAP loss has both tumor-intrinsic and -extrinsic effect. Intrinsically, it leads to the substrate MTA accumulated, which is a natural inhibitor of PRMT5. Extrinsically, MTA exhibits toxicity to T cells suggesting potential immune resistance. To rescue the immune resistance of cancer patients bearing *MTAP* loss, new therapeutic targets need to be discovered. Fortunately, knock-down PRMT5 has been shown to increase T-cell abundance in tumor tissues, highlighting the potential to improve cancer immunotherapy through PRMT5 inhibition. Normally, PRMT5 along with its cofactor S-adenosylmethionine (SAM), methylates arginine residues on proteins in a symmetric fashion. MTA competitively binds to the SAM binding site inhibiting PRMT5's function. Several types of PRMT5 inhibitors (PRMT5i) have been developed for cancer treatment, however, due to the important role of PRMT5 in controlling T cell function, global PRMT5 inhibition could result in immunosuppressive effects. Considering MTA is a natural inhibitor of PRMT5 that only accumulates in *MTAP*-loss tumors, we hypothesize that MTA-cooperative PRMT5 inhibitor, whose effect is dependent on MTA accumulation, can specifically suppress PRMT5 activity in *MTAP*-loss tumors without compromising immune function, and this type of inhibitor can be supplemented with T-cell mediated cancer immunotherapy. In our study, two types of PRMT5i, MTA-cooperative (MRTX1719) and S-adenosylmethoinine (SAM)-competitive (GSK3326595), were selected testing on *Mtap*-loss murine tumor cell lines, which were generated by CRISPR-Cas9-guide RNA knock out (KO). Our results showed that comparing to GSK3326595, MRTX1719 more significantly reduced the proliferation and arginine dimethylation of *Mtap*-loss tumors, while was less toxic for T cell proliferation, arginine dimethylation and anti-tumor function. *in vitro* and *in vivo* T cell-based immunotherapy suggested that MRTX1719 has potential in promoting T cell therapy efficacy and extending survival of mice bearing Mtap-KO tumors. From the mechanistic study, PI3K-AKT signaling pathway was found that specifically enriched in MRTX1719 treated Mtap-KO tumors but not T cells, along with reduction of phospho-AKT protein level. This strongly suggested that MRTX1719 suppresses MTAP loss tumorigenesis through reducing activation of PI3K-AKT signaling pathway, which not happened in T cells, supporting our hypothesis that MTA-cooperative PRMT5i can promote T cell-mediated antitumor response in MTAP loss tumors.

Abrogating CXCR3 Decreases Zika and West Nile Virus Replication

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Flaviviruses cause significant human illness worldwide, leading to over 4 million infections annually. Zika virus (ZIKV) and West Nile virus (WNV) are two flaviviruses that are canonically transmitted by *Aedes* or *Culex* species mosquitoes. While these infections are usually sub-clinical or self-limiting, severe cases can cause adverse neurological outcomes including microcephaly and encephalitis. With climate change and the expanding geographic range of mosquitoes, it is imperative that therapeutics are developed to prevent flavivirus replication and resultant neurological disease. Flavivirus replication is highly regulated by host immune responses, including interferons and interferon-stimulated genes. One such gene, IP-10, signals through the downstream CXCR3 receptor. IP-10 can have pro- or anti-viral effects depending on the context of infection but is typically upregulated in instances of antiviral activity. While IP-10 is upregulated during ZIKV and WNV infections, its role in these infections is unknown. Blocking CXCR3 abrogated ZIKV replication in human prostate cells without altering cellular proliferation or survival. Therefore, we aimed to define CXCR3 antiviral effects against ZIKV and WNV in alternative cell types. We hypothesized that blocking CXCR3 during ZIKV or WNV infection of leukocytes would also result in decreased viral replication. We assessed CXCR3 expression on THP-1 immortalized human monocyte cells by immunofluorescence. Next, we treated THP-1 cells with CXCR3 antagonist prior to infection with ZIKV or WNV and assessed changes in ZIKV and WNV envelope expression by qRT-PCR. There were significant reductions in ZIKV and WNV envelope expression in antagonist-treated cells when compared to untreated controls. Our findings indicate that CXCR3 antiviral activity applies to multiple flaviviruses and occurs in different cell types, indicating inhibition potential across the Flaviviridae family and multiple tropic sites. This work highlights an undescribed host factor limiting ZIKV and WNV infections. Better understanding the mechanism of CXCR3 flavivirus restriction could lead to the development of novel antiviral therapeutics across flaviviruses. Future work will elucidate the antiviral mechanism of CXCR3, including a potential role as a host cell attachment or entry receptor, as well as assess pan-flavivirus inhibition potential. *In vivo* CXCR3 blockade during ZIKV and WNV infections will also be used to evaluate therapeutic applicability and capacity to prevent severe neurological outcomes.

Sex-Biased Tumor Growth in Anaplastic Thyroid Cancer: Interplay Between Microbiome and Immune System

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Thyroid Cancer (TC) displays a distinct sex-bias with a significantly higher incidence in women while men tend to have higher rates of metastasis and overall poorer prognoses at diagnosis. Anaplastic Thyroid Cancer (ATC) is a rare subtype that is infamous for its' malignancy and difficulty to treat. In this study, a novel murine model of ATC was used to examine the influence of sex, age, and the microbiome on anti-tumor immunity. Sex-biased growth is recapitulated in subcutaneous and orthotopic models with male tumors growing 2-3 times larger than females. Compared to females, the tumor microenvironment in males is characterized by a more profound immunosuppressive phenotype with an enhanced number of T cells expressing exhaustion markers (PD-1, CTLA-4, TIM3, and LAG3), regulatory T cells and PDL-1 expressing myeloid cells and fibroblasts. In addition to immunologic differences, young male and female mice have distinct gut microbial communities at baseline and over the course of ATC development, as seen via 16S rRNA sequencing. To examine the impact of the microbiome in these sex-linked differences, fecal microbiome transfer was utilized. Fecal microbiome engraftment from the opposite sex, prior to tumor inoculation, was sufficient to drive tumor growth in a pattern like the donor, regardless of recipient sex, highly implicating the microbiome as an important factor underlying the sex-related differences in ATC progression. Unlike young mice, there is no significant difference in tumor growth in aged male and female mice. Further, they have less pronounced differences in the intratumoral immune compartment and in gut microbial diversity than in young mice. Overall, our data suggest that the interplay between the microbiome and the immune system is an important factor in sex-biased outcomes in TC aggressiveness; thus, proposing immune and microbial modulations as promising alternatives for ATC treatment.

Allogeneic CAR-NKT Cell Therapy with Improved Resistance to Host-Mediated Rejection for CD19 Positive B-Cell Malignancies

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Chimeric antigen receptor (CAR)-T cells have achieved remarkable successes in B-cell malignancies. However, available CAR.CD19 autologous therapies introduce patient-to-patient variability in responses, require lengthy manufacturing, and are expensive. Hence, there is an urgent need for developing allogeneic cell therapies. Invariant natural killer T (NKT) cells are innate T lymphocytes that are not alloreactive and could be used for CAR-redirected allogeneic immunotherapy. Our ongoing phase I clinical trial evaluating allo-CAR.CD19/IL15.NKTs has produced objective responses without significant toxicity, but the therapeutic cells show limited persistence, decreasing the durability of the response. Host-mediated rejection is known to be a major contributor to low effector persistence of allogeneic cell therapies. To protect donor CAR.NKTs from allorejection we engineered NKTs to express a series of 4-1BB-specific alloimmune defense receptors (ADRs) that selectively eliminates alloreactive T and NK cells. A first-generation ADR (ADR1) that harbors a 4-1BB ligand fragment has been reported to prevent allorejection of CAR.Ts. Our preliminary experiments demonstrate that ADRs could be expressed in NKT or CD19.NKT cells and ADR-transduced donor NKT cells evade allorejection in vitro by eliminating host alloreactive T and NK cells. We further hypothesize that second-generation 4-1BB ADRs, which consist of scFv against 4-1BB, could outperform the first-generation ADR in NKTs. Our results indicate that NKTs transduced with one such ADR (ADR2) expand faster than ADR1 transduced cells, suggesting that ADR2 produces less NKT fratricide. Next, we plan to co-transduce NKTs with CD19.CAR with/without IL15 and ADR1 or ADR2. Further, using in vitro assays and an MHC KO mouse model, we aim to identify a CAR+ADR condition that yields a CAR+ADR.NKT product with the highest levels of allorejection resistance and persistence. Results are expected to inform development of "off-the-shelf" NKT cell products for immunotherapy of B-cell malignancies and possibly other types of cancer.

Cathelicidin Modulates the Host Response During Fungal Sepsis

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While the antifungal activity of the antimicrobial peptide cathelicidin against the pathogen *C. albicans* has been well-described *in vitro*, its role during *in vivo* infection has remained enigmatic. We have shown that during systemic infection that loss of CRAMP *in vivo* is protective, as CRAMP-deficient mice (CRAMP KO) survive a lethal dose of *C. albicans* that begins to kill wild-type mice within 48 hours. While in most organs (kidney, spleen, liver, lung) we find negligible differences in fungal colonization and production of cytokines between CRAMP KO and WT mice, we observe significantly lower fungal colonization of CRAMP KO mouse hearts. Reduced fungal burden in the heart is accompanied by a marked abrogation in the production of the inflammatory cytokines and chemokines. In line with this, bone-marrow derived macrophages deficient in CRAMP show a decreased inflammatory response to fungal infection, which cannot be rescued by the addition of exogenous CRAMP. Current work seeks to determine the impact of cathelicidin on cardiovascular function during fungal sepsis. By dissecting the role that cathelicidin plays in modulating inflammation, we aim to better understand how host response contributes to immunopathology during fungal infection.

Amphiregulin Secretion is Ameliorated by Notch Receptors and Cytokines in T-cells

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Background:

Amphiregulin (AREG) is a pivotal regulator of immune responses, cell proliferation, and tissue repair. It can be potential a therapeutic target to regulate immune responses and facilitate wound healing and tissue regeneration in trauma patients. AREG has been implicated in shaping T-regulatory cells (Tregs) and T-conventional cell (T-con) functions, thus it is important to identify pathways involved in AREG production.

Objective:

NOTCH is a transmembrane protein family has been linked as a potential regulator of AREG production. Additionally, AREG production may be influenced by cytokines, such as IL-6, and IL-10. This study aims to investigate and compare the impact of NOTCH and cytokines on AREG production in peripheral T-regulatory and T-conventional cells.

Methods:

In an in vitro setting, peripheral Tregs and T-con cells were isolated and expanded from 3 donors. To study cytokine effect on AREG production, the following were added: IL-6, and IL-10, with and without addition of SAHM1 (NOTCH inhibition). Culture supernant and cells were collected at 48 hours, AREG ELISA and Notch receptors 1-3 expression was also determined using flow cytometry.

Results:

Notch inhibition increased AREG production over a 48-hour period in stimulated T-reg and T-con. Additionally, AREG secreted by stimulated T-regulatory was significantly higher when compared to T-con regardless of NOTCH inhibition. The addition of IL-10 and IL-6 decreases AREG production and Notch receptor expression on T-reg and T-cons.

Results:

The results indicate that IL-10 and IL-6 may decrease AREG production; as a cytokine produced by T-cells, this may serve as a negative feedback loop. Our data suggest that IL-10 and IL-6 cytokine may decrease AREG expression through modifying Notch receptor expression on T-cells.

AREG Concentration pg/ml

Notch receptor expression

A: T-regulatory Cells

B: T-conventional Cells
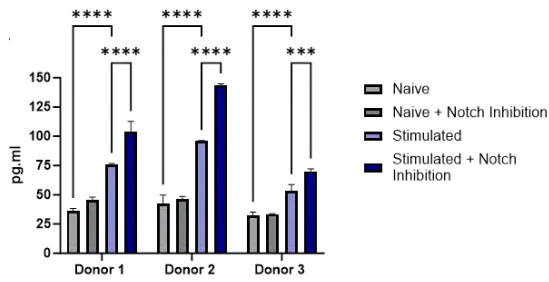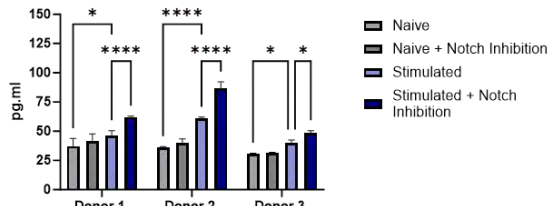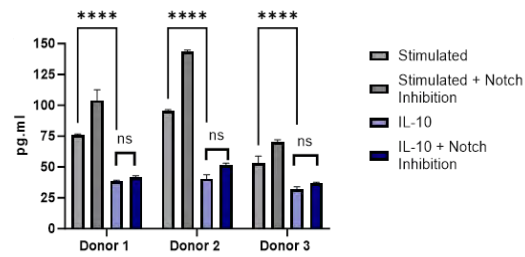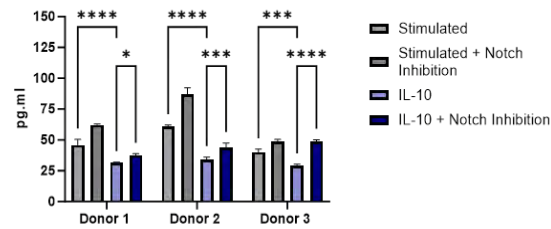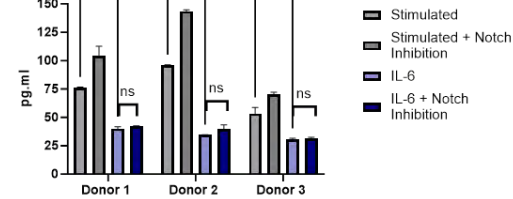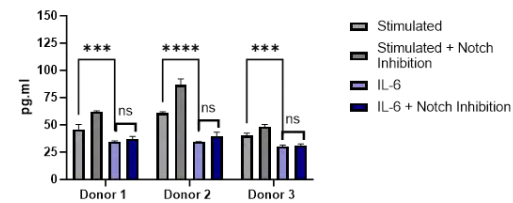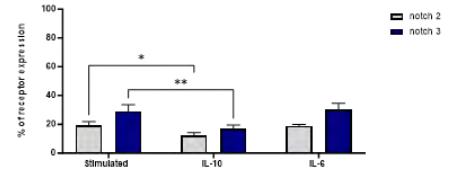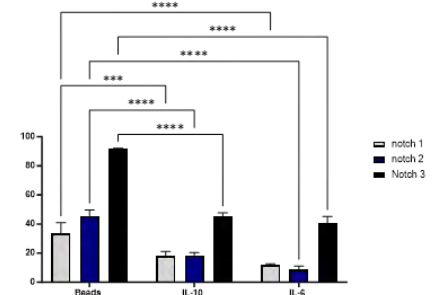
CAR Signaling Domains Determine the Molecular Dynamics at the Immune Synapse Lipid Rafts and Consequently the T Cell Killing Behavior

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Abstract:
CD19-targeting CD28.ζ signaling chimeric antigen receptor (CAR$^{CD28.ζ}$) T cells are associated with rapid tumor cell lysis of B-cell malignancies, contrasting with a more sustained tumor control exhibited by 4-1BB.ζ signaling CAR (CAR$^{4-1BB.ζ}$) T cells. We reasoned that the dynamics of molecular and cellular interactions at the CAR T cell immune synapse (CARIS) could help explain this difference in tumor rejection kinetics.

Our studies show that upon encounter of CD19 but also HER2 expressing cancer cells, CAR$^{CD28.ζ}$ molecules rapidly but transiently interact with CARIS membrane lipid rafts (mLR) mobilizing T cells' microtubular organizing center and lytic granules to form a highly-lethal short-lived CARIS. This high functional avidity was characterized by a sensitivity to modestly expressed target antigens, and a mastery of serial killing. In contrast, gradual accumulation of CAR$^{4-1BB.ζ}$ molecules and LFA-1 at the CARIS mLR built highly adhesive and mechanically tonic synapses resulting in a lengthier Fas ligand-based killing process. This high structural avidity mediated a steady killing pace that relies on the cooperation of robustly expanding T cell effectors.

Our studies demonstrate an influence of signaling domains on molecular events at the CARIS in a manner that could help optimize the use of CAR T cells for solid cancers.

Differential Humoral Immune Responses Against *Orientia tsutsugamushi* Karp and Gilliam Strains Following Acute Infection in Mice

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Scrub typhus is an understudied, life-threatening disease, caused by the intracellular bacterium *Orientia tsutsugamushi* (*Ot*). While cellular immunity is known to be critical for control of infection, the role and status of the humoral immune response remains undescribed. Yet, limited studies have explored germinal center (GC) or B cell responses during *Ot* infection in patients or in experimental animals. This study is aimed at characterizing humoral immune responses during acute scrub typhus and the underlying mechanisms of B cell dysfunction. Our central hypothesis is that infection with *Ot* Karp strain weakens the quality of humoral immune responses by altering kinetics of B cell activation, interactions of T-B cells, and organization of GC during acute disease stages. We demonstrated that *Ot* Karp strain infection caused disorganization of GCs and splenic architecture at severe disease stages. Additionally, we found that *Ot* Karp infection elicited significant downregulation of critical humoral immune response pathways, including B cell receptor signaling, B cell activation, and B cell differentiation. Our studies from lethally infected C57BL/6 mice have revealed dysregulated B cell and GC responses during lethal infection. Current studies employ improved murine models that mimic the spectrum of human scrub typhus disease outcomes to examine the quality of B cell responses during disease progression. Our approaches include in-depth studies of humoral immune responses to *Ot* Karp vs. Gilliam (strains that cause severe disease and self-limiting infection, respectively) infection in mice using flow cytometry, RT-qPCR, and antigen-specific ELISA. Currently, this study has shown a significantly skewed B cell response toward the extrafollicular (EF) response pathway in Karp-infected mice, that was not seen in Gilliam-infected mice. The comprehensive examination of B cell responses during infection with different *Ot* strains and/or mouse models will help build the foundation of knowledge about humoral immunity to scrub typhus.

Use of Biodegradable Pulsatile Release Microparticles to Enable Single-Injection Vaccination for Rabies Post-exposure Prophylaxis

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Although completely treatable, approximately ~60,000 people die annually due to rabies infection as a result of limited healthcare access. Treatment for a potential rabies exposure involves immediately administering rabies immunoglobulin and a vaccine followed by three additional vaccine doses spaced over two weeks. Logistical factors such as travel distance, lost wages, cost of treatment, forgetfulness, and appointments interfering with daily life result in low patient adherence to post-exposure prophylaxis for rabies. Recent advances in microfabrication knows as Particles Uniformly Liquified and Sealed to Encapsulate Drugs (PULSED) enablse the generation of pulsatile drug delivery microparticles. Pulsatile release is characterized by a burst release of a payload after a predetermined delay. By combining multiple microparticle populations, this approach has the potential to deliver multiple doses of the rabies vaccine over two weeks, enabling treatment of potential rabies exposure to be administered during a single healthcare visit. PULSED microparticles are fabricated by creating poly(lactic-co-glycolic acid) (PLGA) open-faced, hollow cylinders using 3D printing and soft lithography. These structures are then filled with dextran-linked fluorescent dye or rabies vaccine and sealed to form a polymeric shell that fully encapsulats the filled material (Figure 1A). *In vivo*, release kinetics were determined using an In Vivo Imaging System to monitor release from particles injected subcutaneously into mice. While the rabies vaccine stability was determined using an enzyme-linked immunoassay that utilizes neutralizing antibodies. Microparticles produced using this method easily fit through a needles as small as 30-gauge (Figure 1B). The temporal delay prior to release can be readily tuned using PLGA formulations with different molecular weights and end groups, enabling payload release 10±1, 15±1, 17±2, and 36±2 days after injection *in vivo* (Figures 1C and D). We also show that we can encapsulate the rabies vaccine without inducing substantial damage, recovering 90±10% of the inactivated virus after sealing. Encapsulating rabies vaccine in PULSED microparticles that mimic the post-exposure prophylaxis for rabies would allow injection of a heterogenious population of microparticles that could be administered at a single healthcare visit to lower patient burden and save lives.
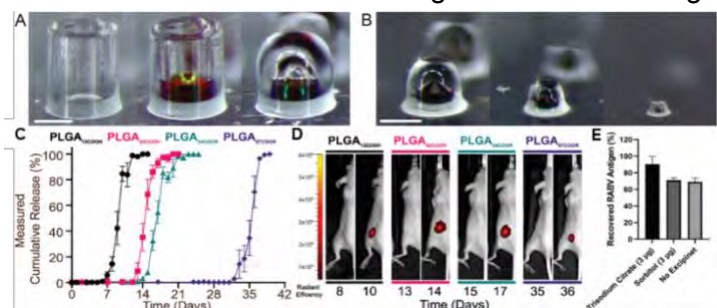
Figure 1. Pulsatile drug delivery for single-injection vaccination of rabies: A) Unsealed, filled, and sealed particles with a diameter of 400 μm B) Sealed microparticles with diameters of 300, 200, and 100 μm. C) *In vivo* pulsatile release of fluorescently conjugated 10 kDa dextran from PLGAs of varying molecular weight and end groups (n=6-9). D) Representative images of *in vivo* release. E) Stability of rabies vaccine through particle fabrication (n=4). Scale bars: white = 200 μm.

Engineering Red Blood Cells to Sequester Drugs and Reduce Therapeutic-Induced Adverse Events

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Although many diseases require the maintenance of a sufficient circulating drug concentration, others diseases, including some cancers, only benefit from drug at the target site. In those cases, drugs at other sites, including in circulation, may not only have no beneficial effect, they may actively cause harm. For example, in oncology, 65% of patients experience severe adverse events from their medications including disorders of the lymphatic, nervous, gastrointestinal, renal, and immune systems[1]. Local administration of drugs can increase therapeutic potency while reducing therapeutic-induced adverse events and extending survival[2–4]. Our lab has previously developed drug delivery systems capable of acting as local depots for extending drug release for days to months with a single injection[5]. However, even with advanced drug delivery systems, rapid clearance from the administration site results in many cancer therapeutics spending a majority of their functional duration not at the target tumor site[6], contributing to changes in B and T cell populations and giving rise to systemic toxicity and adverse events[7]. Red blood cells (RBCs) have been harnessed as drug delivery carriers because of their biocompatibility, long duration in circulation, and inherent ability to carry materials throughout the body[1]. The success of RBCs in drug delivery suggests that a similar approach could be harnessed for drug sequestration. Whereas local delivery increases concentration at the site of action, improving the drug concentration gradient, systemic drug collection and inactivation reduces the concentration in non-target sites, creating an even more favorable gradient. The intratumoral injection of therapeutics paired with the intravenous administration of the drug-sequestering RBCs may allow for the inactivation of off-target drug that escapes the tumor site, maintaining therapeutic efficacy in the tumor while reducing systemic side effects. This drug capture platform has the potential to address a key impediment to effective and safe therapeutics and potentially be tuned to remove a wide variety of drugs. Developing drug capture platforms in tandem with improving local drug delivery systems may offer major improvements in care by reducing the toxicity of current drug doses, enabling clinicians to safely improve doses to better treat disease, or some combination of the two.

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**Force Remodels Mitochondria by Tuning Protein Metabolism in Blood Development**

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Hematopoietic stem cell (HSC) transplant is the standard of care for many hematologic diseases. However, many patients cannot benefit from this potentially curative treatment because they cannot find a suitable donor, contributing to a high level of unmet need. Attempts have been made to generate HSCs *in vitro*, but so far none of these attempts have produced bona fide HSCs suitable for transplant. Scientists continue to look for signals from the niche that promote hematopoiesis, and key answers may lie in examining the role of extrinsic factors that regulate hematopoiesis in the developing embryo.

We show that the physical forces associated with blood flow are critical for regulating metabolic shifts necessary for the specification of HSCs emerging from arterial vessels during embryogenesis. Mutant embryos lacking a heartbeat fail to produce HSCs and only have hematopoietic progenitors with immature mitochondria containing fewer cristae, as determined by electron and super-resolution microscopy. Force generated by blood flow stimulates mitochondrial protein translation, cristae formation, increased mitochondrial membrane potential, and oxidative phosphorylation. These adaptations can be mimicked *ex vivo* by exposing cultured hematopoietic progenitors to force, resulting in increased mitochondrial activity with improved transplantation performance. Single-cell transcriptome and protein analyses indicate that force-responsive PI3K-Akt signaling regulates mTORC1 effectors S6K and 4E-BP1 to promote translation of mitochondrial ribosomes and electron transport chain proteins.
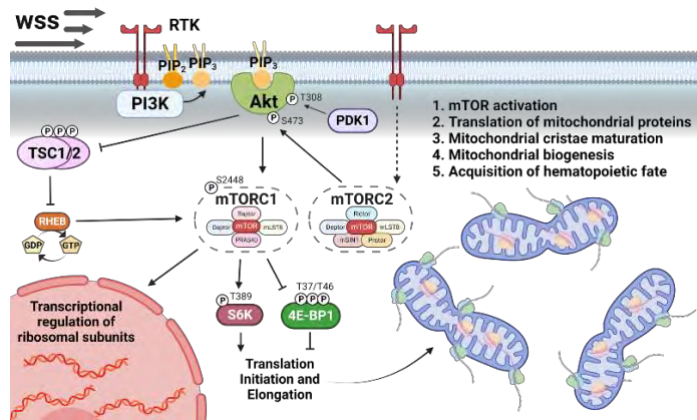
Our work exposes an overlooked role of force in the maturation of mitochondrial machinery essential for HSC emergence and population of the blood system. While *in vitro* specification of HSCs continues to elude us, our study may provide clues to essential flow-sensitive molecular mechanisms that can be leveraged for future HSC engineering.

The Role of CD83 In Modulating Tumor Immune Responses

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Immune checkpoint blockade (ICB) has advanced the treatment of melanoma and other cancer types. Despite the success of ICB, only half of the treated patients experience successful immune responses while remaining patients do not respond to these therapies. Dendritic cells (DC) interact with T cells to mount efficient anti-tumor responses, but solid tumors poorly infiltrated by effector CD8 T cells (eCD8) or highly infiltrated by regulatory T (Treg) cells escape from those anti-tumor responses.

An activated state of intra-tumoral DC characterized by the expression of the chemokine receptor CCR7 has been recently identified and found to be well-conserved between various cancer types in human and mouse. CCR7$^+$DC are known to play a role in mediating tumor immune responses, and they upregulate certain cell surface molecules that enhances their ability to present antigens and induce eCD8 responses. Among these molecules CD83, a CCR7$^+$DC maturation marker with immunomodulatory effects in models of transplantation and autoimmune diseases, has not been studied in tumor microenvironment.

Murine melanoma are better controlled when Tregs are depleted, but those mice expressed lymphadenopathy and lymphoproliferative disorders. Interestingly, in those settings we observed that the levels of CD83 on CCR7$^+$DCs decreased compared to Treg sufficient mice. To better understand the role of CD83 in Tregs and DC, we used Treg specific conditional knock-out of CD83 to abrogate soluble CD83 release from Treg and monitored tumor growth. Compared to control, mice with Treg intrinsic CD83 deficiency had stronger eCD8 responses and better controlled melanoma tumors. Surprisingly, the absence of CD83 on Tregs also reduced CD83 expression on CCR7$^+$DCs, suggesting a possible interaction of CD83 molecules between these cells. These mice did not express lymphoproliferative disorders indicating that CD83 deficient Tregs were not compromised on their suppressive functions.

To decipher the function of CD83 in CCR7$^+$DCs, we used a dual-recombinase CCR7$^+$DC specific CD83-conditional knock-out and observed that these mice better controlled melanoma tumors compared to wild-type. The CD83-deficient CCR7$^+$DCs produced more IL-12 which resulted in an increase of the eCD8 responses. Accordingly, human melanoma single cell-RNA sequencing data showed negative correlation between CD83 expression on CCR7$^+$DC and infiltration of CD8 T cells. In summary, our results demonstrate that the ablation of CD83 molecule resulted in increased anti-tumor immune response. This study explores a novel mechanism of interaction between Tregs and CCR7$^+$DCs and it paves the way for considering CD83 as a new immune checkpoint molecule for cancer treatment.

Dynamic Contact Analysis Of TCRpHLA Complexes

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Understanding the interactions between peptide-HLA (pHLA) complexes and T-cell receptors (TCRs) at a structural level is crucial for developing peptide-based therapeutics and vaccines. However, due to the limited availability of structural data on TCRpHLA complexes, it can be beneficial to conduct computationally less expensive experiments to identify the crucial points of interactions, even in created models. In this study, we used 21 crystal structures of TCRpHLA complexes. Our objective was to obtain the interaction fingerprints of the Complementarity Determining Regions (CDRs) of the TCRs with the surface of the pHLA complex and determine whether a shorter simulation time would be sufficient to extract these fingerprints. Fingerprints were also derived from the static structures, which were used as a reference for the contacts obtained before the simulation. To reduce the required computational resources and accelerate the analysis, we worked with truncated versions of the crystals, containing only the HLA cleft (i.e., α1 and α2), the bound-peptide, and the variable domains of the α and β chains of the TCR (i.e., including the CDRs). We used Gromacs 2021, with Charmm36 force field running in Carya Cluster (RCDC, University of Houston), to obtain 300ns trajectories of the molecular dynamics. We then used the GetContacts package to receive all intermolecular contacts along the simulation and R codes to filter and extract TCR fingerprints by cleaning data noise, reducing dimensionality, and defining data strata. Our simulations showed many interactions with positions 4 and 5 of the peptide, not differing from the static crystallographic structure in this manner. However, other significant differences are observed between static and dynamic data.

Moreover, we noticed that our dynamic data can be divided into two groups based on the RMSD of our simulations. One group stabilizes the simulation between 10 and 25 ns, while the other presents persistent variability beyond this point. By characterizing the differences between these two groups, we can determine the amount of simulation needed to obtain reliable results for TCRpMHC complexes. This approach can help optimize the use of resources and reduce computational expenses for many other structures based on the prior analysis of their static characteristics.

Modulating Alternative Splicing of GSDMB to Enhance Anti-Tumor Pyroptosis

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Pyroptosis is a programmed necrotic cell death induced by pore-forming gasdermin (GSDM) proteins, which can punch holes in plasma membranes and release inflammatory molecules. There are five known active GSDM family members in humans: GSDMA, GSDMB, GSDMC, GSDMD and GSDME. In cancer-associated pyroptosis, granzymes released by killer lymphocytes can remove the C-terminal autoinhibitory domains of GSDMs and cause membrane rupture of tumor cells, further activating anti-tumor immune protection. However, previous studies showed controversial roles of GSDMB in anti-tumor immunity. In fact, there are several GSDMB splicing variants that exhibit different expressions and functions in cells. Therefore, we aim to clarify the function of each GSDMB protein isoform and ask how alternative splicing affects cancer-associated pyroptosis.

GSDMB has five isoforms generated by alternative splicing of exons 6-7. The ectopic expression of each cleaved N-terminal fragment (NT) of GSDMB isoform in HEK293T cells indicated that only GSDMB3 and GSDMB4 isoforms with exon 6 were cytotoxic when they were cleaved by granzyme A. AlphaFold and cryoEM analysis of the protein structure further showed that exon 6 was required for pore formation of GSDMB-NTs. By performing the tumor cell killing assay, we found only GSDMB3/4-expressing HeLa cells died from pyroptosis after the attack by natural killer cells. GSDMB1/2-expressing HeLa cells only died from noninflammatory apoptosis. GSDMB is differently expressed in various cancer types and is highly expressed in some colorectal cancer cell lines. Compared to normal tissues, noncytotoxic GSDMB1/2 are overexpressed, but cytotoxic GSDMB3/4 are suppressed in many tumors, indicating they exert distinct functions in tumorigenesis.

Our results suggest the alternative splicing of GSDMB could be a potential clinical target for cancer treatment. We plan to design splice-switching antisense oligonucleotides (SSOs) to increase the expression of cytotoxic GSDMB isoform in cancer cells and induce effective killer cell-triggered pyroptosis to boost anti-tumor immunity. The splice-switching efficiency of SSO will be tested in human cancer cell lines with high levels of noncytotoxic GSDMBs, and their ability to promote anti-tumor immunity will be further evaluated in humanized mouse models. We believe that our GSDMB SSO intervention would hold great promise for enhancing anti-tumor immunity and could be combined with other immunotherapy for cancer treatment.

Role of TRIM29 in Controlling Intestinal Inflammation

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Abstract:

Enteric virus infection and intestinal inflammation are recognized as a leading cause of deadly gastroenteritis, and inflammasome activation signals control these infection and inflammation. However, the regulatory mechanisms of NLRP6- and NLRP9b-inflammasome signaling in enteric viral infection remain unexplored. In this study, we found that the E3 ligase TRIM29 suppressed type III interferon (IFN-λ) and interleukin-18 (IL-18) production by intestinal epithelial cells (IECs) when exposed to enteric RNA viruses. Knockout of TRIM29 in IECs was efficient to restrict intestinal inflammation triggered by the enteric RNA viruses, rotavirus in suckling mice, and the encephalomyocarditis virus (EMCV) in adults. This attenuation in inflammation was attributed to the increased production of IFN-λ and IL-18 in the IECs from TRIM29-deficient mice. TRIM29 could promote K48-linked ubiquitination and degradation of both NLRP6 and NLRP9b protein, resulting in decreased IFN-λ and IL-18 secretion by IECs. Therefore, targeting TRIM29 could offer a promising therapeutic strategy for alleviating gut diseases.

Cannabidiol Induces Differential Effects on Airway Hyperreactivity and Inflammation in Two Distinct Murine Asthma Models

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Asthma is a chronic inflammatory condition characterized by tissue remodeling, airway hyperreactivity, and immune cell infiltration of the lower airway. The immunological pathogenesis of asthma is complex, but is strongly driven by an adaptive immune response involving the activation and polarization of T helper (Th) cells which coordinate downstream immune responses. Although asthma is generally driven by a Th2 response, more severe endotypes also involve a prominent Th17 response. Th17-predominant asthma is often resistant to standard corticosteroid treatment and other therapies. Therefore, it is crucial to find new methods to modulate inflammation and decrease disease burden in Th17-predominant asthma. Cannabidiol (CBD) is a chemical component of the *Cannabis sativa* plant which interacts with cannabinoid receptors present on many cell types, including most immune cells. CBD has immunomodulatory effects and has been shown to reduce disease burden in models of chronic inflammatory disorders. However, the mechanisms by which CBD affects Th cell development and function are not completely understood. Additionally, it is unknown whether inhaled CBD can be used to suppress inflammation in individuals with standard or steroid-resistant asthma. Using two immunologically distinct murine models of fungal-induced allergic airway disease (AAD), both being models of asthma, we have found that intranasal administration of CBD displays differential effects on cytokine production and airway hyperreactivity (AHR), the primary physiologic consequence of asthmatic inflammation. Our data show that CBD selectively suppresses cytokine production and AHR in Th17-predominant AAD, while failing to suppress cytokine production and AHR in Th2-predominant AAD. Furthermore, we have determined that CBD directly suppresses Th cell proliferation and cytokine production *in vitro*, most strikingly suppressing the production of IL-17. Our data not only provide information about the effects of CBD on different endotypes of allergic airway inflammation and on Th cell function, but also indicate that CBD may have therapeutic potential for the treatment of severe, corticosteroid-resistant asthma.

Engineered Receptor provides Inducible Signal 2 and Signal 3 Co-stimulation to Augment TCR-based Cell Therapies of Cancer

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Cellular immunotherapy using natural and engineered TCR-based T cells produces versatile and highly sensitive tumor targeting in preclinical models. However, their activity in a clinical setting is limited due to the lack of costimulatory signaling (Signal 2) and cytokine availability (Signal 3), which reduces functional persistence of T cells and their clinical benefit. Engineered constitutive cytokine signaling helps boost T-cell persistence but comes with a risk of accelerated T-cell exhaustion or uncontrolled proliferation. We *hypothesized* TCR-based therapies can be enhanced by integrating T cells with **physiologic** costimulatory Signal 2 and a **conditional** Signal 3 resembling natural cytokine signaling.

To test this hypothesis, we engineered a receptor to express on the T cell membrane consisting of an extracellular domain derived from a 4-1BB ligand (4-1BBL) and intracellular signaling domain of the thrombopoietin (TPO) receptor, cMPL, previously shown to emanate gamma-chain cytokine receptor signaling through STAT3 and STAT5 phosphorylation. Upon antigen recognition and TCR stimulation in T-cells, the 4-1BBL-cMPL receptor engages 4-1BB, which is transiently upregulated on T-cell surface upon activation, thus producing Signal 2 through 4-1BB with physiologic intensity and timing. In turn, 4-1BB engagement activates intracellular cMPL signaling of the engineered receptor producing temporary Signal 3 to further aid in costimulation and survival of activated T-cells. This way we provide an inducible co-stimulation system specific to antigen-activated T cells only. Functionally, when tested in T cells expressing a chimeric T-cell receptor (cTCR) targeting a leukemic antigen, co-expression of our engineered receptor on these cells produced 25-fold higher expansion than unarmed cTCR T cells, in an in vitro tumor coculture system. Similarly, when expressed on T cells redirected with leukemia-specific T-cell engager, the costimulatory receptor improved cell expansion by 35-fold, indicating the benefit is not limited to engineered TCRs. When engineered in Virus-Specific T cells (VSTs) targeting EBV infected B-cell lymphoblasts, the 4-1BBL-cMPL receptor co-expressing EBVSTs endured and expanded in a repeat tumor stimulation assay for at least 5 rounds of stimulation. Finally, a single injection of the engineered receptor armed cTCR T cells mounted robust expansion and persistence in the absence of exogenous cytokines in a mouse xenograft model of human leukemia, in which unarmed cTCR T cells failed to provide a durable anti-tumor response. These results suggest the application of the newly developed costimulatory receptor could be extended to diverse TCR-based therapies, to overcome the limited T cell persistence.

A Snapshot of the Systemic Sclerosis Inflammatory Profile from the All of Us Platform

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The All of Us platform encompasses over 700,000 participants with the goal of understanding diseases represented in the US. Systemic sclerosis is an autoimmune disease that causes skin fibrosis due to connective tissue hyperplasia. Fibrosis affects skin, lungs, blood vessels, and the digestive system associated with genetic, environmental, and immune factors. Understanding more about these three aspects is critical to gain a deeper understanding of disease pathogenesis and patient education. The All of Us program data encompasses genomic and electronic health data, under different tiers of access. Genomic data is referenced against the humaGRCh38. ICD10 code M39.4 was use to characterize the All of Us Platform for systematic sclerosis phenotypes. 0.33% of total participants mapped to ICD10 M34.9 (systemic sclerosis). Patients with lung disease represented the highest percentage of patients with equal distribution of systemic sclerosis with polyneuropathy, myopathy, diffuse, and drug-induced systemic sclerosis. IL-17 has pro-and anti-fibrotic affects, yet no genetic variants have currently been curated. High mobility group box 1 (HMGB1) was represented as insertions, single nucleotide variations, and deletions. Electronic health data showed autoantibody levels for PM-SCL-100IgG and PM-SCL-75 that were comparable between men and women, yet lower for PM-SCL-75. Underlying pathology associated with polyneuropathy, myopathy, may point to new clinical determinants of health. Future work should delineate the pro/anti-inflammatory axis and highlight other determinants of health.

KDM6B mediated epigenetic reprogramming of intratumoral myeloid cells regulates response to immune checkpoint therapy in Glioblastoma.

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Abstract

Glioblastoma (GBM)- a disease with dismal overall prognosis demonstrates de-novo resistance to immune checkpoint therapy (ICT). Notably, GBM tumors harbor immune-suppressive myeloid cell subsets which confer therapeutic resistance to ICT. Targeting specific epigenetic pathways to reprogram immune-suppressive myeloid cell subsets into an immune-stimulatory phenotype to improve response to ICT remains largely unexplored. Our aim was to identify key epigenetic factor(s) regulating immune-suppressive pathways in myeloid cells and target these epigenetic factors to overcome myeloid cell mediated resistance to ICT in GBM. Single-cell and spatial transcriptomic analyses of human GBM tumors showed that intratumoral immune-suppressive myeloid cell subsets highly express an epigenetic enzyme known as histone 3 lysine 27 demethylase (KDM6B). Importantly, myeloid cell-specific deletion of *Kdm6b* reduced tumor-burden and improved survival in preclinical models of GBM. In-depth mechanistic studies demonstrated alterations in the epigenetic and transcriptomic landscapes of *Kdm6b*-deficient myeloid cells with concomitant increase in the interferon response, phagocytic ability, and antigen-presentation. Further, pharmacological inhibition of KDM6B in a murine model of GBM recapitulated the functional phenotype of the genetic model and improved survival following anti-PD1 therapy. Overall, this study delineated the impact of KDM6B as a critical epigenetic regulator of the phenotype and function of myeloid cells and demonstrated its importance as a potential therapeutic target to improve response to anti-PD1 therapy.

Mechanisms of Inflammatory Caspase Activation in Sickle Cell Disease

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Sickle cell disease (SCD) is an inherited red blood cell disorder that impacts millions of people worldwide. Patients with SCD experience chronic lysis of red blood cells which results in elevated levels of free heme, the small molecule co-factor of hemoglobin. Free heme induces inflammation, a central feature of most SCD complications. Our lab showed that the pro-inflammatory proteins caspase-1 and caspase-4 are activated in macrophages exposed to heme. Activation of these proteins leads to IL-1β release and pyroptosis, a form of inflammatory cell death. We sought to understand how heme activates this pathway and to identify potential therapeutic targets for mitigating inflammation in patients with SCD. Using an imaging-based caspase activation reporter, we found that caspase-4 activation is upstream of caspase-1 activation. We also found that caspase-4 is required for both pyroptosis and IL-1β release after heme exposure while caspase-1 is only required for IL-1β release. Together, this indicates caspase-4 is the apical step in this pathway and a promising drug target for blocking heme-induced inflammation in SCD. Other known activators of caspase-4 directly bind to the protein to induce auto-cleavage into its active form. To determine if heme acts similarly, we performed molecular docking experiments and found two predicted heme-binding sites in the p10 catalytic subunit of caspase-4. We next confirmed that heme directly interacts with caspase-4 in vitro. Using a pull-down assay with heme conjugated to agarose beads, we observed heme bound to purified caspase-4 and to casapase-4 in macrophage cell extract. To determine if heme binding to caspase-4 results in activation, we incubated heme with purified caspase-4 and found that heme induces auto-cleavage of caspase-4. Thus, caspase-4 is a direct heme receptor; heme-induced caspase-4 activation leads to caspase-1 activation, IL-1β release and cell death. Our future work will elucidate the functional effects of heme binding to caspase-4 in mouse models of sickle cell disease.

Targeting Tumor-Associated Macrophages to Treat Triple-Negative Breast Cancer

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Breast cancer is the most prevalent cancer and accounts for the second-highest cancer mortality rate in women. The triple-negative breast cancer (TNBC) subtype has the worst prognosis. With a lack of defined therapeutic targets, Adriamycin + cyclophosphamide + taxane chemotherapy is the standard of care, but it often results in the later development of resistant metastatic disease. Recently, immune checkpoint blockade (ICB) has been approved for TNBC. CD8 T cell infiltration is a predictive marker for ICB that is associated with a better prognosis, whereas suppressive myeloid cell infiltration is associated with a worse prognosis. Therefore, a novel approach to the treatment of TNBC is the targeted re-education of the TIME to sensitize tumors to immunotherapies, including ICB. Tumor-associated macrophages (TAMs) are suppressive myeloid cells that are common targets for solid tumor TIME re-education. Previously, MerTK inhibition (MerTKi) has been shown to reprogram TAMs in various cancer subtypes. Here we couple MRX-2843, a novel MerTKi, with standard of care chemotherapy CTX. These studies aim to identify MRX-2843 as a novel TAM reprogramming therapy, as well as to evaluate the clinical value of coupling with chemotherapy. To accomplish these goals, we will use a novel *in vitro* macrophage polarization assay in conjunction with single-cell RNA sequencing (scRNA-seq) data generated from our well-characterized *in vivo* preclinical TNBC mouse tumor models. The p53-null Balb/c tumors are infiltrated with macrophages and include claudin-low, basal, and luminal-like TNBC tumor subtypes. **We hypothesize that treating MRX-2843 will re-educate the TIME, leading to an anti-tumoral immune response. Further, macrophage heterogeneity will contribute to variability in therapeutic response, and its characterization may identify predictive macrophage markers and potentially druggable targets, including targets for ICB.** We will use scRNA-seq data to characterize macrophage heterogeneity for multiple TNBC subtypes, determine the changes in these populations after treatment with MRX-2843, and characterize the TIME of these treated tumors. Further, to evaluate the value of coupling TAMr with standard-of-care chemotherapy, we will combine MRX-2843 with an immunomodulatory dose of cyclophosphamide for long-term treatment of tumor-bearing mice. As TAMr therapy is a novel and understudied modality, we will also use high-throughput screening of TAMs using a machine learning algorithm to identify novel TAMr therapeutic drugs. We will then validate and test the top candidates with our in vitro TAM reprogramming assays, as well as treat tumor bearing mice. Overall, these studies will identify changes in TAM heterogeneity during and after TAMr therapy while simultaneously determining the clinical significance of coupling these drugs with standard-of-care chemotherapy.

Identification of Single Cell RNA Signature Immune-Related Pathways in γδ T cells in Shrimp Allergy

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Rationale: Shellfish allergy is one of the most common food allergies worldwide and third most common in US children. It has been reported that γδ T cells play a regulatory role in peanut allergy. At present, the role and immunologic mechanism of γδ T cells in shrimp allergy remain unclear. This research aims to investigate transcriptional pathogenic pathways in γδ T cells in shrimp allergy.

Methods: Peripheral blood mononuclear cells (PBMCs) from shrimp allergic patients (SA, n=2) and healthy control subjects (HC, n=3) were incubated with shrimp tropomyosin (TM) 1 ug/ml for 24 hrs. Single-cell RNA sequencing (scRNA-seq) of pooled PBMCs was performed (10X Genomics® gene expression 5v2 kit). Differentially expressed genes were analyzed by gene ontology (GO) Biological Process® and Kyoto Encyclopedia of Genes and Genomes® (KEGG) pathway tools.

Results: Differentially expressed genes analysis showed upregulation of IL-10R in total PBMC from shrimp allergic patients, upregulation of TGF-β1, lower IL7R in SA-stimulated vs HC-stimulated γδ T cells ($p < 0.00005$), and downregulation of gene expression of IRF and NFKB1A ($p < 0.0001$, $p < 0.0003$, respectively) in stimulated vs unstimulated HC γδ T cells. We found upregulation of lymphocyte-mediated cytotoxin signaling pathways in SA γδ T cells ($p < 0.00003$), while cytokines-mediated and myeloid differentiation in HC ($p < 0.0007$) in response to TM stimulation.

Conclusions: γδ T cells play a regulatory role in pathogenesis of shrimp allergy and may through signaling pathways of lymphocyte-mediated cytotoxin signaling pathways and cytokines-mediated and myeloid differentiation. This study provides new insights into molecular mechanisms of γδ T cells in SA.

An Immunosuppressive Role for Platelet Protein Phosphatase 1c a in Cancer Pathophysiology

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Lung cancer, the second most common cancer in both men and women in the US with estimated 234,580 new cases and 125,070 deaths in 2024. Cancer is often marked by dysregulated signaling in tumor cells, including amplification of the catalytic subunit of protein phosphatase 1 alpha (PP1cα). However, besides the intrinsic alterations in tumor cells, signaling crosstalk between tumor cells, blood platelets and immune cells in the tumor microenvironment can also accelerate cancer progression. Tumor induced platelets display quantitative changes in PP1cα at proteomic level, and we also observed increased PP1cα protein in platelets from human lung adenocarcinoma patients and in the mice with experimental metastasis. To test how platelet PP1cα impact experimental metastasis, we implanted LL2 (lung cancer) and B16F10 (melanoma) via tail vein in wild type (WT) and platelet specific PP1cα $^{-/-}$ mice and studied tumor metastasis to lungs. In both lung cancer and melanoma models, loss of platelet PP1cα reduced experimental tumor burden. Platelets suppress CD8 and CD4 T cells function, in part, via an expression of a docking latent TGF-β receptor called glycoprotein A repetitions predominant (GARP), which concentrates latent TGF-β on the cell surface and enhance latent TGF-β activation becoming TGF-β, a critical immunosuppressive cytokine. Compared to the WT, tumor bearing platelet specific PP1cα $^{-/-}$ mice had reduced GARP protein level. Certainly, we observed reduced TGF-β signaling in the lung tumor sections from PP1cα $^{-/-}$ mice by immunohistochemistry staining with phospho Ser 423 and Ser 425 SMAD3 antibody. Meanwhile we were also initiated to understand better how immune cells are recruited to the tumor site. For that, we investigated innate and acquired immune cell distribution in the lung of the wild type and Platelet specific PP1cα $^{-/-}$ mice. Compared to wild type mice, platelet specific PP1cα $^{-/-}$ mice showed reduced PD-1$^+$ CD8 T cells, three weeks following LLC and B16F10 implantation. These findings are independent of the immune suppressive microenvironment, because the relative abundance of immunosuppressive cells of the myeloid origin, namely monocytic myeloid-derived suppressor cells were not altered in tumor bearing PP1cα $^{-/-}$ mice. Since high PD-1 expression on T cells is linked with immune exhaustion, lower PD-1 expression in CD8 T cells in PP1cα $^{-/-}$ mice may support a more efficient CD8 T response in this model. Thus, platelet PP1cα exerts an immunosuppressive role and facilitate cancer progression. These studies suggest simultaneous blockade of platelet PP1cα along with immune check points may provide exclusive opportunities to optimize cancer immunotherapy.

The Role of the BRD4/ZDHHC-1/STING Axis on Allergic Asthma Development

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Rationale: Early exposures to environmental estrogens (EEs) are associated with increased asthma prevalence. We have previously identified the enhanced expression of bromodomain-containing protein 4 (BRD4)/ zinc finger HHC-1 (ZDHHC1)/stimulators of IFN genes (STING) after EE exposure. We aimed to investigate the effects of EEs on the development of allergic asthma using our EE exposure model with the BRD4/ZDHHC1/STING axis.

Methods: Female BALB/c mice received 10 μg/ml bisphenol A (BPA), bisphenol S (BPS), or vehicle control in their drinking water during pregnancy until their pups were weaned. Half of the dams received peritoneal injections of STING inhibitor, C-176. The pups were sensitized with an intentionally "suboptimal" low dose of ovalbumin (Ova) on postnatal day 4, 1% Ova inhalation on days 18-20, and asthma phenotype was assessed on day 22. Non-sensitized female pups were saved and bred with non-exposed male mice at 8 weeks of age. The subsequent pups were sensitized, and asthma phenotype was examined up to the fourth generation.

Results: F1-F4 pups from EE-exposed dams developed asthma phenotype. Pups from C-176 treated dams had decreased response to their sensitization compared to non-treated controls. Airway hyperresponsiveness and IgE anti-Ova were lower in pups with C-176 treatment.

Conclusions: Early exposure to EEs, including BPA and BPS, promotes the development of experimental asthma, possibly through the BRD4/ZDHHC1/STING axis. The immune alterations may be epigenetically perpetuated, causing multigenerational effects.

Immune Checkpoint Inhibitor-Mediated Colitis: Mechanistic Insights and Therapeutic Targets

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Immune checkpoint inhibitors (ICIs) have revolutionized cancer treatment by reinvigorating T cell anti-tumor functionality through the blockade of inhibitory signals such as PD-1 and CTLA-4. Though ICIs have improved outcomes in many types of cancers, their use is often accompanied by uncontrolled inflammation that can occur in any organ. Of these, ICI-colitis poses a particular threat as it occurs in about 14% of patients on combination ICIs and is one of the most commonly fatal and debilitating immune-related adverse events (irAEs). The mechanisms underlying irAE pathogenesis are not well understood and preclinical models are necessary to gain this insight. In this study, we have designed a murine model of subclinical colitis that fully develops only after ICI administration, as evidenced by decreased body weight, shortened colon lengths, and deteriorated colon structure. Notably, there is an accumulation of T and B cells in the colon accompanied by an increase in B cells and a decrease in T cells in the mesenteric lymph nodes (mLN). Colitis severity is correlated with enhanced IL17 production in $CD8^+$ T cells, IFNγ and TNFα expression in $CD4^+$ T cells, and IL-17A and IL-6 production in B cells. Blockade of B cells, $CD8^+$ T cells, and implicated cytokines limit ICI-colitis development. Additionally, blockade of α4β7 integrin limits colonic inflammation and appears to sequester these involved T and B cells in the mLN, suggesting that intestinal inflammation is reliant on their trafficking to the colon. Additionally, fecal microbiome transfer (FMT) from healthy mice to mice with subclinical colitis deters the accumulation of these pathogenic cell subsets when treated with ICIs, implicating gut dysbiosis as an important factor in ICI-colitis development and as a therapeutic target. Overall, our data suggest that dysbiosis and/or epithelial injury elicit an inflammatory immune response that is rapidly exacerbated and lead to target organ tissue inflammation/damage upon introduction of ICIs.

Elucidating The Mechanism of CAR NKT Cell Antitumor Activity in Syngeneic Neuroblastoma Models

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Despite remarkable successes in patients with B cell malignancies, T cells expressing chimeric antigen receptors (CARs) do not yet mediate high levels of objective responses in patients with solid tumors. Unlike T cells, natural killer T (NKT) cells traffic effectively to tumor sites, as our group has shown with neuroblastoma (NB), and are an attractive option for CAR-redirected targeting of solid tumors. In addition to CAR-mediated tumor killing, NKTs are hypothesized to mediate indirect antitumor activity by targeting CD1d+ tumor-supportive macrophages in the tumor microenvironment and promote host NK and T cell responses via maturing dendritic cells. However, the effects of CAR NKT on the TME have not been evaluated in an immunocompetent model. Thus, we developed a syngeneic murine NB model, which exerted a 100% tumor take rate in WT C57BL/6J mice with a stable B7H3 expression. B7H3 is overexpressed in multiple pediatric tumor types, including NB, making it a suitable target for CAR-mediated therapy. First, we demonstrated that NKT cells expressing a B7H3-CAR eliminated B7H3+ NB cells *in vitro* and that CAR constructs with CD28 co-stimulation performed better than CARs with 4-1BB co-stimulation. Additionally, the co-expression of IL15 along with CAR (15.CAR) enriched the proportion of central memory cells after repeated tumor challenges. NKT cell therapy produced no toxicity in the preliminary in vivo experiments. We also detected a higher number of NKT cells expressing 15.CAR compared with CAR alone in peripheral blood of the treated mice. Future experiments will be designed to mechanistically evaluate how CAR-NKT and 15.CAR-NKT interact with the intact immune system in our model that will inform development of a more effective NKT-based immunotherapy of neuroblastoma.

Stomach Microenvironment Facilitates Ascaris Hatching and Infection

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Ascariasis (roundworm) is the most common parasitic helminth infection globally and can lead to significant morbidity. Children become infected with *Ascaris spp.* via oral ingestion of eggs. It has long been assumed that Ascaris egg hatching and larval translocation across the gastrointestinal mucosa to initiate infection occurs in the small intestine. Here, we show that *Ascaris suum* larvae hatched in the host stomach in a murine model. Larvae utilize acidic mammalian chitinase (AMCase; acid chitinase; Chia) from chief cells and acid pumped by parietal cells to emerge from eggs on the surface of gastric epithelium. Furthermore, antagonizing AMCase and gastric acid in the stomach decreases parasitic burden in the liver and lungs and attenuates lung disease. Given Ascaris eggs are chitin-coated, the gastric corpus would logically be the most likely organ for egg hatching, though this is the first study directly evincing the essential role of the host gastric corpus microenvironment. In addition, we show that the gastric corpus downregulates AMCase and acid in response to repeated *A. suum* infection to reduce larval migration. These findings point towards potential novel mechanisms for therapeutic targets to prevent ascariasis and identify a new biomedical significance of AMCase in mammals.

TRIM29 Deficiency Mitigates Viral Myocarditis by Attenuating PERK-driven ER Stress and ROS Responses

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ABSTRACT
Viral myocarditis, an inflammatory disease of the myocardium, is a significant cause of sudden death in children and young adults. The current coronavirus disease 19 pandemic emphasizes the need to understand the pathogenesis mechanisms and potential treatment strategies for viral myocarditis. Here, we found that TRIM29 was highly induced by cardiotropic viruses and promoted protein kinase RNA-like endoplasmic reticulum kinase (PERK)-mediated endoplasmic reticulum (ER) stress, apoptosis, and reactive oxygen species (ROS) responses that promote viral replication in cardiomyocytes *in vitro*. TRIM29 deficiency protected mice from viral myocarditis by promoting cardiac antiviral functions and reducing PERK-mediated inflammation and immunosuppressive monocytic myeloid-derived suppressor cells (mMDSC) *in vivo*. Mechanistically, TRIM29 interacted with PERK to promote SUMOylation of PERK to maintain its stability, thereby promoting PERK-mediated signaling pathways. Our findings offer novel insight into how cardiotropic viruses exploit TRIM29-regulated PERK signaling pathways to instigate viral myocarditis, suggesting that targeting the TRIM29-PERK axis could mitigate disease severity.

T-Cell Dysfunction Associated with the *LRRK2* Mutation in the Pathogenesis of Parkinson's Disease

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Although the Parkinson's Disease (PD) community has increasingly studied the involvement of the immune system, it has been largely limited to evaluating the innate immune system, such as inflammatory cytokines and microglia. Recently, T cell infiltration in post-mortem brain sections was reported in PD patients, which has spurred research into the role of T cells in these diseases over the past five years. Emerging results have unveiled heightened α-synuclein (syn)-specific CD4^{+} T-cell responses in patients, suggesting potential T-cell-mediated adaptive immune responses to neuron-derived antigens. Leucine-rich repeat kinase-2 (*LRRK2*) mutations are well-recognized genetic risk factors in PD, with the G2019S mutation, resulting in aberrantly enhanced kinase activity, being the most common pathogenic mutation. Although increased LRRK2 activity was found in immune cells from PD patients, the impact of *LRRK2* G2019S mutation on immune functions, particularly T-cell immunity, remains unclear. Therefore, we focus on exploring whether *LRRK2* G2019S mutation contributes to PD pathogenesis via altering CD4^{+} T-cell functions. To fill this knowledge gap, we generated a new T cell receptor (TCR) transgenic mouse strain bearing *LRRK2* G2019S knock-in mutation, OT-II/LRRK2 (Refer to Mut). As CD4^{+} T cells from OT-II mice specifically recognize ovalbumin, this new strain enables us to explore the impact of *LRRK2* G2019S mutation on T-cell functions in an antigen-specific manner. We found that the abundance and proliferation of major immune subsets in spleen tissue from Mut mice are comparable to wild-type (OT-II, Refer to WT) control. However, when we characterized T cell differentiation in these two strains, T cells derived from Mut mice displayed increased Th2 (IL-4) and decreased Th9 (IL-9) and Treg (Foxp3^{+} %) differentiation. Th1 differentiation of Mut T cells remains unchanged. *LRRK2* G2019S mutation significantly altered the expression levels of master transcription factors (TFs) for T cell differentiation. Specifically, Mut T cells displayed an increase in mRNA expression of *Gata3* (TF for Th2), and a decrease in expression of *Irf4* and *Foxp3* (TFs for Th9 and Treg, respectively). Mechanistically, *LRRK2* mutation decreased IL-9 production and Treg cell population through the JAK/STAT3 signaling. On the other hand, LRRK2-selective inhibitor suppresses Th2 and promotes Th9 and Treg differentiation in both murine and human CD4^{+} T cells. In conclusion, we have successfully established new genetically modified mouse models to evaluate the potential role of LRRK2 in modulating T cell function, specifically CD4^{+} T cell differentiation, warranting further studies to evaluate the impacts of altered T cell differentiation led by *LRRK2* mutation in dopaminergic neuron damages.

Immune Dysregulation in a Mouse Model for Lysinuric Protein Intolerance

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Lysinuric protein intolerance (LPI) is an inborn error of metabolism associated with growth delay, osteoporosis, renal disease, pulmonary complications, urea cycle dysfunction, and immune dysregulation. This disorder arises from biallelic, pathogenic variants in *SLC7A7*, which encodes the light subunit of the y$^+$L amino acid transporter (y+LAT1). The y+LAT1 transporter facilitates the efflux of arginine, lysine, and ornithine from intestinal epithelial cells, renal tubular cells, and myeloid lineage hematopoietic cells. Impaired transport of arginine and ornithine in the intestine and kidneys reduces the circulating levels of these amino acids, leading to urea cycle dysfunction. However, the mechanisms underlying other phenotypes remain unclear. To investigate these mechanisms, we generated a *Slc7a7* knockout (*Slc7a7*$^{-/-}$) mouse model, recapitulating LPI features, including the biochemical phenotype, growth failure, and renal disease. During our studies of osteoporosis in LPI, we performed mRNA sequencing in long bones from *Slc7a7*$^{-/-}$ vs. wild type littermates. Our results revealed evidence of dysregulation of the innate immune response, activation of multiple cytokine pathways, and increased *Il1b* expression. Nevertheless, the model limits the study of immune dysregulation due to failure to thrive and poor survival. To address this limitation, we created a conditional knockout mouse model (*Slc7a7*$^{f/f}$) to further investigate immune dysregulation in LPI. Given the high expression of *SLC7A7* in hematopoietic cells of the myeloid lineage, we hypothesized that impaired amino acid transport in these cells drives the immune phenotype in LPI. To test this hypothesis, we deleted *Slc7a7* in all hematopoietic cells by crossing to a Vav-iCre transgenic mice. Consistent with our hypothesis, Vav-iCre+; *Slc7a7*$^{f/f}$ male mice exhibited significantly enlarged spleens and a shift towards M1 macrophages in the bone marrow. The thymus in these mice was also enlarged, in addition to increased thymic CD8+ T cells and T cell progenitors, as well as decreased thymic CD4+ T cells. Our results suggest that immune dysregulation in LPI may arise from impaired amino acid transport in hematopoietic cells. Future studies will explore which specific cell type within the hematopoietic system drive immune dysregulation in LPI and elucidate the mechanisms by which disordered ornithine, arginine, and lysine transport impair immune cell functions.

Aerobic Glycolysis Licenses the Effector Differentiation Potential of Stem-like CD4+ T Cells

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CD4+ T cells play a critical role in both transplant rejection and anti-tumor responses. Despite their significance, the exact mechanisms regulating effector CD4+ T cell responses remain elusive. This study aims to elucidate the underlying mechanisms driving the effector differentiation of CD4+ T cells and to identify potential therapeutic strategies for promoting transplant tolerance and augmenting anti-tumor responses. Alloreactive TEa (TCR transgenic, TCR Vα2Vβ6, B6 background) CD4+ T cells were adoptively transferred into B6 mice following BALB/c heart transplants. Seven days post-transplantation, the transferred TEa cells from spleens and heart grafts were subjected to examination using single-cell RNA sequencing (scRNA-seq). Clustering analysis of scRNA-seq data unveiled the existence of two prominent stem-like precursor clusters (TCF1hiLy108hi) within alloreactive TEa cells in spleens, while a major effector cluster (TCF1loCXCR6+) was identified in heart allografts. Deletion of TCF1 in TEa cells significantly diminished the Ly108hiCXCR6– stem-like population but did not result in transplant acceptance. Importantly, the Compass analysis delineated 1,497 distinct metabolic reactions within 79 subsystems, highlighting significant differences between stem-like and effector TEa cells. The latter demonstrated improved metabolic activity, with numerous reactions positively correlated with the expression of effector genes such as *Cxcr6*, *Nkg7*, *Tnfrsf18*, and *Gzmb*. Notably, glycolysis, specifically the Lactate Dehydrogenase A (LDHA)-driven pyruvate-to-lactate conversion, was remarkably active in effector cells. Strikingly, the conditional deletion of the glycolytic enzyme LDHA in T cells (*Ldha*fl/fl*Cd4*-Cre) led to heart transplant tolerance without the need for immunosuppressants. Mechanistically, *Ldha* deletion halted most glycolytic activities, suppressed the expression of key effector genes (e.g., *Gzmb*, *Ifng*, *Cxcr6*), and prevented H3K27ac deposition at effector gene loci (e.g., *Ifng*, *Cxcr6*, *Nkg7*) in TEa cells post-transplantation. Consequently, *Ldha*–/– alloreactive CD4+ T cells predominantly maintained a stem-like state, failed to differentiate into TCF1–CXCR6+ effectors, and did not infiltrate allografts, thereby preventing transplant rejection. Moreorver, in a CD4+ T cell adoptive transfer model targeting melanoma, stem-like CD4+ Trp1 cells demonstrate the capability to eliminate established B16F10 melanoma through LDHA-mediated aerobic glycolysis. In conclusion, LDHA plays a pivotal role as a metabolic regulator in CD4+ T cell responses. Strategically directing interventions towards glycolytic pathways emerges as a compelling approach to achieve transplantation tolerance and enhance anti-tumor responses.