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Message from the Chairman

It is a great pleasure for me to welcome you to the Sue Golding Graduate Division (SGGD) and our Department of Microbiology and Immunology at the Albert Einstein College of Medicine. Our laboratories in the Department of Microbiology and Immunology cover a wide range of topics spanning the fields of virology, bacteriology, host immune responses to infection and cancer, inflammation and autoimmune disease. The department warmly and enthusiastically welcomes PhD candidates and postdoctoral fellows who are interested in pursuing research projects and potentially developing careers in these areas. I welcome all new students in the SGGD and postdoctoral candidates to contact me or any of the department's faculty directly to explore the terrific range of opportunities available to you in the Department of Microbiology and Immunology.

My best wishes for success in your new adventure!

Professor & Chairman
Department of
Microbiology and Immunology

MICROBIOLOGY AND IMMUNOLOGY

FACULTY
2024-2025

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Jacquline Achkar, Professor Medicine/ID, Joint Appt. w/M&I	Jacqueline.achkar@einsteinmed.edu	413	Forchheimer	430-8763
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MICROBIOLOGY AND IMMUNOLOGY

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2024 – 2025

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Chong, Alex (Berney)	430-3023	Forchheimer 406
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Cole, Erin (Goldstein)	430-2156	Forchheimer 408
Corrigan, Devin T. (Zang)	430-4154	Forchheimer 405
Courturier, Nicole (Lauvau)	678-1595	Price Center 508
DeMouth, Megan (Chandran)	430-8552	Golding 403
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Enright, Jennifer (Lauvau)	678-1595	Price Center 508
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Gromish, Matthew (Herold)	839-7460	Van Etten 6A04A
Gualdron, Tania Jaimes (Herold)	839-7460	Van Etten 6A04A
Guillen, Erik (Lauvau)	678-1595	Price Center 508
Held, Ardith (Herold/ Almo)	839-7460	Van Etten 6A04A
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Lamcaj, Sara (Goldstein)	430-2607	Forchheimer 408
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Pulanco, Marc Christopher (Zang)	430-4154	Forchheimer 405

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MICROBIOLOGY & IMMUNOLOGY

GRADUATE STUDENTS

2024 – 2025

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DR. JACQUELINE M. ACHKAR

Jacqueline Achkar is an Infectious Diseases trained physician-scientist with an additional master's degree in clinical research methods, and a Professor of Medicine, Microbiology and Immunology. Her NIH-funded translational research program focusses on tuberculosis (TB) serology, biomarker discovery, and protective antibody responses and functions against Mycobacterium tuberculosis (Mtb). She is one of the pioneers contributing to the paradigm shift that antibodies have protective functions against Mtb and her group has demonstrated protective in vitro and in vivo functions of Mtb antigen-specific human antibodies.

Active tuberculosis (TB) is a transmissible respiratory disease that is caused by uncontrolled Mycobacterium tuberculosis (Mtb) infection. Surpassing HIV, it is, after SARS-CoV-2, the leading cause of death from a single pathogen worldwide. To control this major global public health problem, accurate and simple point of care diagnostics, additional options of antituberculous therapies, and more effective vaccines are urgently needed. Dr. Achkar's research has the potential to inform these all of these critically important fields.

Dr. Achkar is further the Associate Director for Translational Research Training of our institutional Clinical Research Training Program, the Principal Investigator and, together with Dr. Kartik Chandran, the co-Program Director of Einstein's T32 Training Program in Geographic Medicine and Emerging Infections, the Director of Global Health Research, and a member of and mentor for the Sub-Saharan African Network for TB/HIV Research Excellence (SANTHE). In 2024, Dr. Achkar was further elected as a US CDC TB elimination champion. She has many national and international collaborations with investigators from a broad range of expertise such as clinical research, epidemiology, modeling and statistics, microbiology, molecular biology, biochemistry, and biodesign, and has extensive experience in training and mentoring students, fellows, and junior faculty members.

PUBLICATIONS

1. Liu, Y, Chen T, Zhu Y, Furey A, Lowary TL, Chan J, Bournazos S, Ravetch JV**, Achkar JM***. Features and protective efficacy of human monoclonal antibodies targeting Mycobacterium tuberculosis. JCI Insight 2023. Oct 23;8(20):e167960. PMID: 37733444
2. Ishida E, Corrigan DT, Chen T, Liu Y, Kim RS, Song L, Rutledge TM, Magee MD, LaBaer J, Lowary TL, Lin PL, **Achkar JM***. Mucosal and systemic antigen-specific antibody responses correlate with protection against active tuberculosis in nonhuman primates. EBioMedicine 2024; Jan:99:104897. PMID: 38096687
3. Chen T, Blanc C, Liu Y, Ishida E, Singer S, Xu J, Joe M, Jenny-Avital ER, Chan J, Lowary TL, **Achkar JM***. Capsular glycan recognition provides antibody-mediated immunity against tuberculosis. Journal of Clinical Investigation 2020; J Clin Invest. 2020 Apr 1;130(4):1808- 1822. doi: 10.1172/JCI128459.J Clin Invest. 2020. PMID: 31935198
4. Nguyen MV, Jenny-Avital ER, Burger S, Leibert EM, **Achkar JM***. Factors Associated With Sputum Culture-Negative vs Culture-Positive Diagnosis of Pulmonary Tuberculosis. JAMA Network Open 2019 Feb 1;2(2):e187617. doi: 10.1001/jamanetworkopen.2019.7617 (16)
5. Younis H, Kerschbaumer I, Moon J-Y, Ryung S. Kim R, Blanc CJ, Chen T, Wood R, Lawn S, **Achkar JM***. Combining urine lipoarabinomannan with antibody detection as a simple non-sputum-based screening method for HIV-associated tuberculosis. PLOS ONE 2019; Jun 25;14(6):e0218606, PMID:31237915 (10)
6. Song L, Wallstrom G, Yu X, Hopper M, Van Duine J, Steel J, Park J, Wiktor P, Khan P, Brunner A, Wilson D, Jenny-Avital ER, Qiu J, LaBaer J, Magee DM, **Achkar JM***. Identification of antibody targets for tuberculosis serology using high-density nucleic acid programmable protein arrays. Mol Cell Proteomics. 2017; 16(4 suppl 1):S277-S289. PMID: 28223349 (7)

DR. STEPHEN BAUM

DR. JINAN BEHNAN

Area of Research: ***Glioblastoma, Tumor Stroma, Origin of tumor macrophages, Mesenchymal subtype, Immunotherapy, Drug screening***

Behnan Lab-Tumor Stroma: Our aim is to characterize the tumor stroma in Glioblastoma (GBM), the most aggressive and treatment-resistant brain tumor. We were the first in the world to report the recruitment of endogenous Mesenchymal stem cells (MSCs) in glioma (Behnan et al. Stem Cells, 2014) and to characterize the mesenchymal subtype in GBM patients (Behnan et al. Oncogene, 2017). Our observation indicated that the Mesenchymal subtype is divided into two subgroups: one induced by recruited cells and microenvironment, and another tumor cell per se expressing Mesenchymal properties, suggesting that brain derived MSCs/perivascular cells may be the tumor origin (Behnan et al. Brain 2019; Behnan et al. Oncogene, 2017).

Our particular focus is on understanding the biology of recruited noncancerous cells to the tumor, primarily the immune cells and mesenchymal stem cells/perivascular progenitors in different GBM subtypes, and to define the origin of different recruited cell populations, and their interaction with cancerous cells to solve the complexity and heterogeneity of this devastating tumor. Simultaneously, we are working on establishing a translational therapeutic treatment for GBM through combining immunotherapy with other target therapy to change the immunosuppressive microenvironment and eradicate cancer cells. With our extensive knowledge in human Glioma stem cells (Behnan et al. Sci Rep, 2016), we aim to establish a drug screening library to test the specificity of drug response among different GBM subtypes. We will be using immune competent glioma mouse models, transgenic models utilizing different techniques including flow cytometry, confocal microscopy, 2 photon microscopy, and low threshold ultrasound. We are looking for collaborative integrative approaches with other investigators to reach innovative treatment and achieve our ultimate goal of developing treatments for brain tumor patients.

PUBLICATIONS

1. Mondal I#, Das O#, Sun R, Gao J, Yu B, Diaz A, **Behnan J**, Dubey A, Meng Z, Eskandar E, Xu B, Lu O.R*, Ho W.S*. PP2Ac Deficiency Enhances Tumor Immunogenicity by Activating STING-Type I Interferon Signaling in Glioblastoma. ***Cancer Res***. 2023 Aug doi: 10.1158/0008-5472.CAN-22-3382. PMID: 37219874.

2. Hu Y#, Jiang Y#, **Behnan J**, Ribeiro M.M, Kalantzi C, Zhang M, Lou D, Häring M, Sharma N, Okawa S, Del Sol A, Adameyko I, Mikael Svensson M, Persson O, and Ernfors P. Neural-network learning defines glioblastoma features to be of neural crest perivascular or radial glia lineages. ***Science Adv*** 2022 Jun. doi: 10.1126/sciadv.abm6340.

3. Guo M*, Goudarzi K, Abedi S, Pieber M, **Behnan J**, Sjöberg E, Zhang X.M, Ernfors P, Harris R.A, Bartek J, Lindström M, Nistér M, Hägerstrand D*. SFRP2 induces a mesenchymal subtype transition by suppression of SOX2 in glioblastoma. ***Oncogene*** (2021). https://doi.org/10.1038

4. **Behnan J***, Finocchiaro G, Hanna G. The Landscape of Mesenchymal Signature in Brain tumors. ***Brain****:* a journal of neurology 2019 142;4 847-866

**Corresponding author*

5. **Behnan J***, Stangeland B, Langella T, Finocchiaro G, Tringali G, Meling T, Murrell W. Identification and Characterization of New Source of Adult Human Neural Progenitors. ***Cell*** *Death and Disease* (2017) **8**, e2991; doi:10.1038/cddis.2017.368.

**Corresponding author*

6. **Behnan J***, Stangeland B, Hosainey SA, Joel M, Olsen TK, Micci F, Glover JC, Isakson P, Brinchmann JE (2017). Differential propagation of stroma and cancer stem cells dictates tumorigenesis and multipotency. ***Oncogene***, 36 (4), 570-584. PubMed 27345406.

*Corresponding author

7. **Behnan J***, Stangeland B, Langella T, Finocchiaro G, Murrell W, Brinchmann JE (2016) Ultrasonic Surgical Aspirate is a Reliable Source For Culturing Glioblastoma Stem Cells ***Sci Rep***, 6, 32788. PubMed 27605047. *Corresponding author

8. **Behnan J***, Isakson P, Joel M, Cilio C, Langmoen IA, Vik-Mo EO, Badn W (2014) Recruited brain tumor-derived mesenchymal stem cells contribute to brain tumor progression ***Stem Cells***, 32 (5), 1110-23. PubMed 24302539. *Corresponding author

9. Fayzullin A, Tuvnes FA, Skjellegrind HK, **Behnan J**, Mughal AA, Langmoen IA, Vik-Mo EO (2016). Time-lapse phenotyping of invasive glioma cells ex vivo reveals subtype-specific movement patterns guided by tumor core signaling. ***Exp Cell Res***, 349 (2), 199-213. PubMed 27515001

10. **Behnan J**, Grieg Z, Joel M, Ramsness I and Stangeland B*. Gene knockdown of *CENPA* reduces sphere forming ability and stemness of glioblastoma initiating cells. ***Neuroepigenetics*** 7, (2016) 6-18

11. Joel M, Mughal AA, Grieg Z, Murrell W, Palmero S, Mikkelsen B, Fjerdingstad HB, Sandberg CJ, **Behnan J**, Glover JC, Langmoen IA, Stangeland B (2015). Targeting PBK/TOPK decreases growth and survival of glioma initiating cells in vitro and attenuates tumor growth in vivo. ***Mol Cancer***, 14, 121. PubMed 26081429

12. Sandberg CJ, Vik-Mo EO, **Behnan J**, Helseth E, Langmoen IA (2014). Transcriptional profiling of adult neural stem-like cells from the human brain ***PLoS One***, 9 (12), e114739. PubMed 25514637

DR. JOAN W. BERMAN

Dr. Berman's laboratory examines the mechanisms that mediate HIV entry into the CNS and how viral and inflammatory mediators damage neurons and other CNS cells. More than 40 million people worldwide are HIV infected. As a result of antiretroviral therapies, HIV infected people are living longer. HIV enters the CNS early after infection and despite therapy, persists within the CNS. Prevalence of NeuroAIDS and its associated cognitive impairment is increasing. An understanding of mechanisms that mediate these effects are critical to the development of therapeutic strategies.

HIV infection of the CNS can have devastating consequences, often resulting in cognitive impairment and severe neurological complications. The basis of this impairment is poorly understood. Although its development is associated with early viral infiltration of the CNS, the number of activated monocytes/macrophages within the CNS appears to be a better indicator of neurologic compromise than viral load, suggesting that leukocyte infiltration and cognitive impairment are tightly correlated. How infected monocytes cross the blood brain barrier (BBB) and infiltrate the CNS is not well understood. This process is critical to the development of NeuroAIDS as it brings leukocytes into the brain where they activate and infect microglia, and effect damage to the BBB and other CNS cells. The mechanisms of HIV-infected monocyte transmigration across the BBB have only been minimally characterized. We are characterizing several of the steps in this transmigration process using a tissue culture model of the human BBB. We analyze the mechanisms that mediate attachment and diapedesis of HIV-infected monocytes across the BBB to identify markers that contribute to brain infection and BBB disruption, such as adhesion molecules, tight junction and adherens proteins, chemokines and their receptors. The lab has a major translational component, examining sera and CSF from HIV infected individuals for predictors of cognitive impairment, as well as patient cells for unique markers of this impairmentand for their ability to transmigrate across the blood brain barrier. We examine tissue from HIV-infected individuals for altered proteins. The overall goal is to identify targets for therapeutic intervention to limit the entry of HIV into the CNS.

Many HIV-infected people who abuse drugs have more extensive CNS damage associated with significant cognitive impairment. As many drugs of abuse cause an increase in extracellular dopamine, we examine the effects of dopamine on HIV infection of macrophages. We demonstrated that dopamine increases HIV infection of human macrophages and are addressing the mechanisms by which dopamine causes this increase as well as alterations in macrophage function. We also study the impact of buprenorphine and methadone,therapies for Opiate abuse, in the context of NeuroAIDS.

PUBLICATIONS

Eugenin EA, Martiney JA, Berman JW. (2019) The malaria toxin hemozoin induces apoptosis in human neurons and astrocytes: potential role in the pathogenesis of cerebral malaria. Brain Res. 2019 Jul 2:146317. doi: 10.1016/j.brainres.2019.146317.
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Williams, DW, Calderon, TM, Lopez, L, Carvallo, L, Gaskill, PJ, Eugenin, EA, Moregllo, S, Berman, JW. (2013) Mechanisms of HIV Entry Into the CNS: Increased Sensitivity of HIV Infected CD14+CD16+ Monocytes to CCL2 and Key Roles of CCR2, JAM-A, and ALCAM in Diapedesis. PLOS One. Jul 26;8(7):e69270.

Williams, DW, Eugenin, EA, Calderon, TM, Berman, JW. (2012) Monocyte Maturation, HIV

Susceptibility, and Transmigration Accross the Blood Brain Barrier are Critical in HIV Neuropathogenesis. Journal of Leukocyte Biology, Mar;91 (3):401-15.

Buckner CM, Calderon TM, Williams DW, Belbin TJ, Berman JW. (2011) Characterization of monocyte maturation/differentiation that facilitates their transmigration across the blood-brain barrier and infection of HIV: Implications for NeuroAIDS. *Cell Immunol;* 267(2):109-23.

Eugenin E.A., Clements J.E, Zink M, and Berman J.W.(2011) HIV infection of human astrocytes disrupts blood brain barrier integrity by a gap junction dependent mechanism. The Journal of Neuroscience. 31(26):9456-65.

King JE, Eugenin EA, Hazleton JE, Morgello S and Berman JW (2010) Mechanisms of HIV Tat Induces phosphorylation of NMDA Receptor Subunit 2A in Human Primary Neurons: Implications for NeuroAIDS Pathogenesis. *Am.J Pathology*, June17:2819-30.

Roberts TK, Eugenin EA, Morgello S, Clements JE, Zink MC and Berman JW, (2010) PrP^{C}, the Cellular Isoform of the Human Prion Protein, is a Novel Biomarker of HIV-Associated Neurocognitive Impairment and Mediates Neuroinflammation, *Am. J.Pathology*, Oct 2010; 177(4):1848-60.

Gaskill PJ, Calderon TM, Luers AJ, Eugenin EA, Javitch JA, Berman JW, (2009) Human Immunodeficiency Virus (HIV) Infection of Human Macrophages Is Increased by Dopamine. A Bridge between HIV-Associated Neurologic Disorders and Drug Abuse,.*Am J Pathol*. September 175(3):1148-59.

Eugenin EA, Osieki K, Lopez L, Goldstein H, Calderon TM, Berman JW, (2006) CCL2/Monocyte chemoattractant protein-1 mediates enhanced transmigration of human immunodeficiency virus (HIV)-infected leukocytes across the blood-brain barrier: a potential mechanisms of HIV-CNS invasion and NeuroAIDS. *J Neurosci* 26(4):1098-1106.

DR. MICHAEL BERNEY

Novel antibacterial tactics are urgently needed to combat the rapid global rise of **antibiotic resistance.** The Berney lab focuses on one of the major global killers and important representatives of the antibiotic resistance and persistence issue, *Mycobacterium tuberculosis* (*Mtb*). *Mtb* kills around 1.8 million people each year, more than any other infectious disease. This is particularly alarming because the number of multidrug-resistant *Mtb* clinical isolates is rapidly increasing. To tackle this problem, our fundamental understanding of TB biology needs to be greatly advanced. In order to develop novel strategies to tackle TB, the Berney lab is focused on 1. gaining a detailed mechanistic understanding of how *M. tuberculosis* adapts metabolically and bioenergetically to the host environment to identify new drug targets, and 2. get a mechanistic understanding of how *Mtb* becomes tolerant or resistant to antibiotics. Our research priorities and methodologies are:

Research priorities:
- Studying the **host-pathogen metabolic interaction** and uncovering new **nutritional immunity** mechanisms
- Elucidating **antibiotic resistance mechanisms** in bacterial pathogens and understanding the **molecular determinants of antibiotic persistence**
- Identifying new **vulnerable pathways in *M. tuberculosis* bioenergetics and anabolism** as target spaces for TB chemotherapy.
- Discovery of **new lead compounds** with novel mechanisms of action

Research methodology:
- Metabolomics and classic biochemistry
- Transcriptomics
- Systems biology
- Mycobacterial genetics
- High resolution respirometry
- Microbial physiology, culture-independent detection methods
- Animal models of Tuberculosis disease

PUBLICATIONS

Mulholland CV, Wiggins TJ†, Cui J†, Vilchèze C, Rajagopalan S, Shultis MW, Reyes-Fernández EZ, Jacobs Jr. WR, **Berney M***
Propionate prevents loss of the PDIM virulence lipid in Mycobacterium tuberculosis.
Nature Microbiology 2024 Jun;9(6):1607-1618. doi: 10.1038/s41564-024-01697-8.

Adolph C, Cheung CY, McNeil MB, Jowsey W, Williams ZC, Hards K, Harold LK, Aboelela A, Burjaorski RS, Buckley BJ, Tyndall JDA, Li Z, Langer JD, Preiss L, Meier T, Steyn AJC, Rhee KY, **Berney M**, Kelso MJ, Cook GM.
A dual-targeting succinate dehydrogenase and F1Fo-ATP synthase inhibitor rapidly sterilizes replicating and non-replicating Mycobacterium tuberculosis
Cell Chemical Biology 2024 Apr 18;31(4):683-698.e7. doi: 10.1016/j.chembiol.2023.12.002.

Kalia NP, Singh S, Hards K, Cheung CY, Sviriaeva E, Banaei-Esfahani A, Aebersold R, **Berney M**, Cook GM, Pethe K. *M. tuberculosis relies on trace oxygen to maintain energy homeostasis and survive in hypoxic environments.*
Cell Reports 2023 Apr 26;42(5):112444. doi: 10.1016/j.celrep.2023.112444. Online ahead of print.PMID: 37115669 .

Girotto MA, Handschin G, Ortmayr K, Campos AI, Gillet L, Manfredi P, Mulholland C, **Berney M**, Jenal U, Picotti P and Zampieri M. *CRISPRi meets metabolomics: a platform for rapid functional annotation of compound libraries* ***Nature Chemical Biology*** 18, 482–491 (2022). https://doi.org/10.1038/s41589-022-00970-3

Michael Shultis, Claire Mulholland, **Berney M*** Are all antibiotic persisters created equal? ***Frontiers in Cellular and Infection Microbiology - Bacteria and Host.*** (2022), 12:933458.

Hasenoehrl E, Wiggins T, **Berney M*** Bioenergetic inhibitors and antibiotic efficacy in Mycobacterium tuberculosis In*: The Bioenergetics of Mycobacterial-Host Interactions* ***Frontiers in Cellular and Infection Microbiology - Bacteria and Host.*** (2021), 10 (611683) https://doi.org/10.3389/fcimb.2020.611683

Lee BS, Hards K, Engelhart C, Hasenoehrl EJ, Kalia N, Mackenzie J, Sviriaeva E, Chong SMS, Manimekalai M, Koh V, Chan J, Xu J, Alonso S, Miller M, Steyn A, Grüber G, Schnappinger D, **Berney M**, Cook M, Moraski G, Pethe K. Dual inhibition of the terminal oxidases eradicates antibiotic-tolerant Mycobacterium tuberculosis ***EMBO Molecular Medicine*** (2021) 13:e13207, https://doi.org/10.15252/emmm.202013207

Hasenoehrl E, Sajorda D, Berney-Meyer L, Johnson S, Tufariello J, Fuhrer T, Cook GM, Jacobs WR, **Berney M.*** Derailing the aspartate pathway of ***M. tuberculosis*** to eradicate persistent infections ***Nature Communications*** 10 (1), 1-12

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Essential roles of methionine and S-adenosylmethionine in the autarkic lifestyle of Mycobacterium tuberculosis **Berney M***, Berney-Meyer L, Wong K, Chen B, Chen M, Kim J, Wang J, Chan J, Wang F,

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Featured with a spotlight article in Trends in Microbiology

Full publist:
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DR. EVA BILLERBECK

The Billerbeck laboratory is focused on understanding the immune system of the liver during virus infection and fatty liver disease. Inflammatory liver diseases such as chronic viral hepatitis and non-alcoholic steatohepatitis (NASH) are leading causes for the development of liver cirrhosis and hepatocellular carcinoma (HCC).

As a major metabolic organ of the body the liver is prone towards immune tolerance as it is constantly exposed to gut-derived blood rich in bacterial and dietary antigens. The liver is also enriched in various tissue-resident innate, innate-like and adaptive immune cell populations, such as Kupffer cells, natural killer (NK) cells, invariant natural killer T (iNKT) cells, mucosal-associated invariant T (MAIT) cells and CD4+ and CD8+ T cell subsets. This unique immunological microenvironment may play an essential role in controlling the outcome of a hepatic virus infection as well as the development of immunopathology and liver disease progression during inflammatory liver disease.

It is our aim to understand how different immune cells subsets and their interactions in this tissue-specific environment contribute to the opposing outcomes of: 1) viral clearance and protection from secondary infection versus establishment of chronic viral infection and 2) tissue protection and repair versus development of immunopathology and progressive liver disease.

However, studying these mechanisms is notoriously difficult. Access to human liver tissue, in particular during acute viral infection, is extremely limited. Clinically relevant human hepatitis viruses A-E have a narrow host tropism to the human liver and immune-competent small animal models do not exist. Given these limitations we have a longstanding interest in the development of immune-competent mouse models for the study of hepatotropic virus infections and liver disease.

Interestingly, in recent years various hepatitis C virus (HCV)-related animal viruses were discovered in horses, bats or rodents, which opened the door for the development of HCV surrogate models. In 2014, an HCV-related rodent hepacivirus, named Norway rat hepacivirus (NrHV) was discovered in wild rats of New York City (*Firth et al. mBio 2014*). Subsequently, we showed that NrHV can establish a hepatotropic infection in common immune-competent laboratory mouse strains. We could also show that NrHV infection in mice shares several virological and immunological key features with HCV infection in humans (*Billerbeck et al. Science 2017*).

Using the novel NrHV mouse model and mouse models of diet-induced fatty liver disease we now aim to gain new insight into protective and detrimental hepatic immune mechanisms during inflammatory liver disease. We are further interested in the development of mouse models that reliably recapitulate human end-stage liver disease, such as cirrhosis and HCC. Our long-term goal is to translate basic findings from the mouse models to the human liver and to develop new strategies for HCV vaccine design or immune-therapeutic treatment options for liver disease.

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* Equal contribution

DR. CURTIS BREWER

Area of Research: ***Biochemical and biophysical studies of lectin-glycan and glycan-glycan interactions***

Cell surface carbohydrates have been demonstrated to be involved in a variety of biological recognition phenomena including cellular recognition and adhesion, regulation of inflammation, control of cell growth and metastasis. Although the structures of many of these carbohydrates have been elucidated, relatively little is known about their molecular recognition properties other than their interactions with glycosylases and lectins. Lectins are carbohydrate-binding proteins that are widely found in nature including plants, animals and pathogenic organisms. Lectins and the cell surface glycans of glycoproteins and glycolipids play important roles in cellular homeostasis and innate and adaptive immunity. Our research includes characterizing the biophysical and biochemical properties of lectins and their interactions with multivalent cellular glycans. We are also investigating the self-binding properties of carbohydrate tumor antigens and have presented evidence for their involvement in oncogenesis. Techniques used to explore these interactions include isothermal titration microcalorimetry, x-ray crystallography, atomic force microscopy and optical tweezers.

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DR. ROBERT BURK

Human Papillomavirus (HPV) and Microbiome Translational Science: Molecular Epidemiology, Pathogenesis and Evolution.

The main focus of the Burk laboratory is to understand viral-host evolution and the emergence of HPV types that are highly pathogenic and cause multiple cancers in humans (e.g., cervix and oropharynx). In addition, the lab is also testing hypotheses on the role of epigenetic changes in the viral and host (human) genome and its relationship to precancer and cancer development. Concomitant with viral-host relationships is a new emerging area of interest, the cervical microbiome/mycobiome and its relationship to viral-host interactions and other outcomes. These investigations extend from clinical studies where we obtain exfoliated cervix cellular material (Pap cells) and evaluate the HPV genome, CpG methylation and the composition of the microbiome to cell-based biochemistry studies of viral proteins and molecular evolution of viral sequences.

Studies on the human microbiome continue to expand in our laboratory. We have pioneered collection and analyses of the gut microbiome and oral microbiome in 2 large population based epidemiological studies that encompass populations in the Bronx and throughout the US. Having collected over 10,000 gut microbiome samples from these longitudinal studies, we are well positioned to investigate the role of the microbiome in human disease. The two populations include the largest Hispanic cohort in the US and the largest HIV cohort.

PUBLICATIONS: (representative from >500 peer-reviewed publications)

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DR. KARTIK CHANDRAN

As our world grows more interconnected and humans impinge on the few remaining wild habitats, infections caused by the accidental transmission of viruses from their natural animal hosts to humans are increasingly of concern. The unprecedented 2013–2015 Ebola virus disease epidemic in western Africa and the COVID-19 global pandemic provide particularly apt examples. Few specific antiviral treatments are available for these and other emerging agents, and our ability to develop them is challenged by a poor understanding of exactly how viruses co-opt our own cells at the molecular level.

The Chandran Lab at Einstein strives to understand this molecular warfare between virus and cell, and to apply what we learn to the development of antiviral treatments. Filoviruses, such as Ebola virus and Marburg virus; bunyaviruses, including hantaviruses and nairoviruses; flaviviruses, including yellow fever virus and Powassan virus; coronaviruses, including SARS-CoV-2 and related bat-borne agents; and poxviruses, including vaccinia virus, are major topics of study in our group. Working collaboratively with our partners on three continents, we have helped uncover critical host factors required for viral invasion, including the long-sought Ebola receptor, Niemann-Pick C1 (NPC1) and the New World hantavirus receptor, protocadherin-1 (PCDH1). Some of our other recent and ongoing research questions and interests include:

- Genetic and phenotypic screens and biochemical approaches to identify critical host factors for viral infection
- Roles of genetic variation in host-encoded factors—in NPC1, for example—on the susceptibility of humans and animals to viral infection and the likelihood of animal-to-human 'host-jumping' events
- Discovery and development of human antibody therapeutics to prevent and treat viral infections
- Engineered antibodies as therapeutics to target cryptic viral epitopes
- Library-based approaches to define virus-host interfaces and the mechanisms of antiviral antibody action
- Design and evaluation of broadly active antiviral vaccines

SELECTED PUBLICATIONS

(¶, PhD or MD/PhD students. *, corresponding author)

Mechanisms of Ebola virus entry and infection:

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DR. JOHANNA P. DAILY

Our primary research interest is in *Plasmodium falciparum* pathogenesis. Patients infected with this parasite can be completely asymptomatic or develop severe disease resulting in death. The goal of our research has been to define the molecular mechanisms that underlie this variation in disease outcomes in *P. falciparum.* Toward this goal, we have developed a new pathogenesis model through the analysis of *in vivo* parasite biology and associated host factors using a whole genome approach. We have identified novel parasite biology when it resides in the human host; this biology has not been reported under *in vitro* cultivation and may play a role in enhanced virulence and/or transmission capacity. We use the animal model of malaria to understand the etiology of coma in cerebral malaria and to identify drugs that reduce the brain swelling, which could be tested in future clinical studies. Thus we combine human field based translational studies in cohorts infected with malaria in Africa with animal model and experimental work using molecular biology, whole transcriptional, metabolomic and cellular approaches in the laboratory to improve malaria outcomes.

I. Define factors that result in coma in cerebral malaria.
II. Characterize the mechanisms of brain swelling and screen drugs to lessen brain swelling in the animal model of cerebral malaria using MRI, histopathology and metabolomic screening.

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DR. FELIPE DIAZ-GRIFFERO

key words: HIV-1 uncoating and reverse transcription, restriction factors TRIM5alpha TRIMCyp, transportin-3 (TNPO3), CPSF6, SAMHD1, MxB, SERINC5, elite controllers, and HIV-1 T cell restriction factors.

My research program is focused on understanding early events of HIV-1 infection such as uncoating, reverse transcription and nuclear import. To this end, we have exploited a group of proteins that are expressed by the host, and block HIV-1 infection at early stages. These proteins, known as restriction factors, have allowed us to understand fundamental processes in the HIV-1 life cycle. Besides assisting the understanding of fundamental problems on HIV-1 biology, restriction factors represent a new frontier in the search for an effective HIV-1 cure. The following sections explain our past findings, ongoing and planned research.

1) HIV-1 Uncoating

HIV-1 uncoating occurs early in infection and is the shedding of monomeric capsid from the HIV-1 core, which is composed of 1500 monomers of capsid protein assembled into a conical structure containing the RNA viral genome. Our investigations revealed, contrary to an old dogma, that HIV-1 reverse transcription occurs before or during uncoating but not after (Roa et al., 2012) (Fig. 1). Furthermore, we demonstrated that genetic or pharmacological inhibition of reverse transcription inhibits the uncoating process during infection (Yang et al., 2012). These experiments suggested that internal rearrangements inside the core start the uncoating process. In agreement, we found that cytosolic extracts stabilized the HIV-1 core during infection in vivo and in vitro (Fricke et al., 2013a). Overall, our work suggests that HIV-1 cores are stable in the cytosol, and that initiation of uncoating is triggered from inside the core.

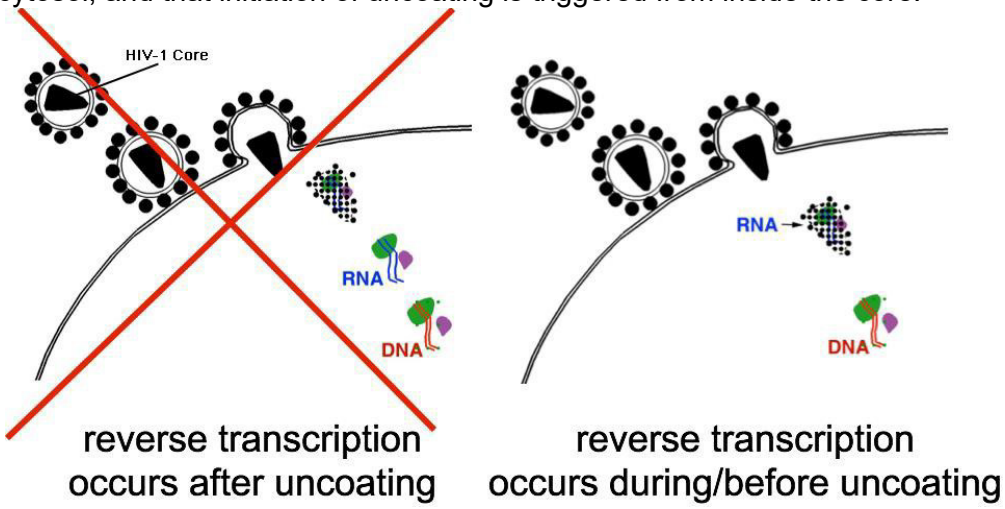

Figure 1. Current model for the occurrence of HIV-1 reverse transcription and uncoating. Our investigations showed that HIV-1 reverse transcription is completed inside the viral core during/before unocating. This is in stark contrast of a past dogma that suggested that reverse transcription occurs after uncoating.

The study of HIV-1 uncoating in vitro has been hindered by the unstable nature of the HIV-1 core outside the cellular environment. This evidence together with work mentioned above

suggests that the HIV-1 core is stabilized by cellular factors. Future work on this area will use biochemical and genetic approaches to identify factors that stabilize the HIV-1 core in the cellular environment. To this end, we will biochemically isolate HIV-1 cores from infected cells and identify the proteins associated to the core by mass spectrometry. We will compare the protein content of HIV-1 cores stabilized by different conditions: using reverse transcription inhibitors (Yang et al., 2012), viruses containing a defective reverse transcriptase enzyme (Yang et al., 2012), the microtubule disruptive drug nocodazol (Lukic et al., 2014; Malikov et al., 2015), cells expressing cytoplasmic CPSF6(Fricke et al., 2013b), and cells expressing MxB/Mx2(Fricke et al., 2014). As a negative control, we will mock isolate cores from cells expressing rhesus TRIM5a, which accelerates uncoating (Diaz-Griffero et al., 2007a; Perron et al., 2007; Stremlau et al., 2005). The assays we have developed to study capsid stability in vitro and in vivo will be used to confirm these interactions (Fricke et al., 2013a). Finally, the contribution to uncoating and infection will be evaluated in cells where the candidate proteins are knockout using the Cas9/CRISPR technology that is already working in our lab. Finding proteins that stabilize the HIV-1 core during infection will provide fundamental understanding on the uncoating process of HIV-1.

2) TRIM5α

The HIV-1 restriction factor TRIM5α is composed of four domains: RING, B-box-2, coiled-coil and PRYSPRY domains (Fig. 2A). To understand the contribution of these different domains to restriction, we have solved the structure of the RING, B-Box-2 and PRYSPRY domains (Biris et al., 2013; Diaz-Griffero et al., 2009; Lienlaf et al., 2011; Roa et al., 2012). Our structure-function studies revealed: 1) the RING domain provides E3 ligase activity, which is necessary for restriction(Lienlaf et al., 2011; Roa et al., 2012), 2) the B-box-2 domain regulates the ability of TRIM5a to form higher-order complexes(Diaz-Griffero et al., 2009; 2007b), which is an essential function for the ability of TRIM5α to form an array of protein in the surface of the core (Fig.2B)(Ganser-Pornillos et al., 2004). 3) the PRYSPRY domain is the domain that comes in direct contact with the HIV-1 core (Yang et al., 2014). In summary our findings suggested that the rhesus macaque protein TRIM5α binds to the surface of the HIV-1 core by forming an array protein (Fig. 2B). Formation of this complex recruits Ubc13, which is an E2 enzyme required for restriction (Pertel et al., 2011). Subsequently, an unknown activity leads to acceleration of uncoating (Diaz-Griffero et al., 2007a; Stremlau et al., 2006). Although, we have recently solved the structure of Ubc13 interacting with the RING domain (Yudina et al., 2015), the mechanism and energy source by which this complex leads to acceleration of uncoating is unknown (Fig.2B).

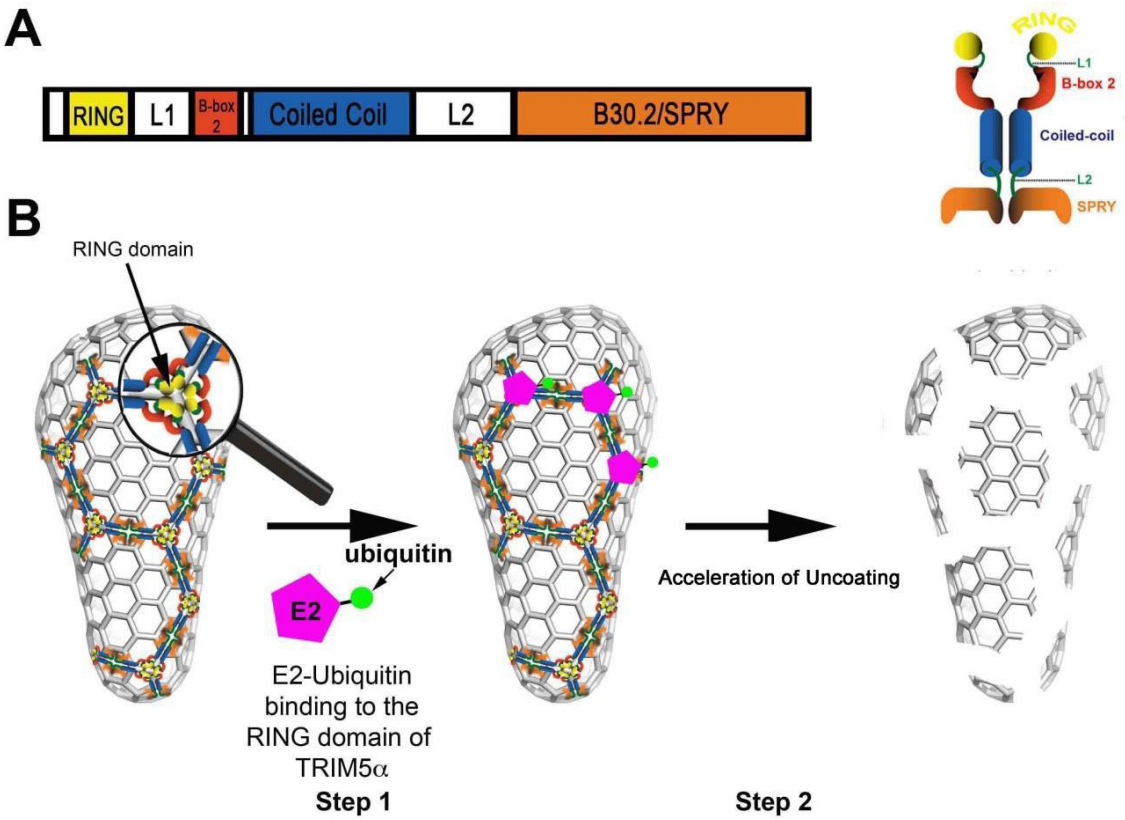

Figure 2. Inhibition of HIV-1 infection by TRIM5α. (A) The different domains of TRIM5α are shown, and a small cartoon depicting the TRIM5α protein is shown on the right side. **(B)** TRIM5a proteins assembled forming a hexagonal pattern on the surface of the HIV-1 core, and the RING domain of TRIM5α recruits an E2 enzyme (Ubc13). Subsequently the core is disassembled (acceleration of uncoating) and infection is aborted. The mechanism and source of energy for this process is unknown.

Interestingly, the structure of the PRYSPRY domain, which is the domain that directly interact with the HIV-1 core, exhibit a flexible loop in the region that interacts with the HIV-1 core (Fig. 3), as established by genetic experiments (Li et al., 2006; Yap et al., 2005). These observations suggested that movement of the loop is providing the energy necessary for the complex to accelerate uncoating. Future experiments will test the hypothesis that a flexible loop is required for acceleration of uncoating. To this end, we will identify TRIM5α mutations on the PRYSPRY domain that decrease the flexibility of the loop but preserve binding to the HIV-1 core. These particular variants will be tested for their ability to block HIV-1 and accelerate uncoating in human cells. These studies will be complemented by experiments that will measure the ability of the PRYSPRY domain mutants in solution to disassemble in vitro assembled HIV-1 CA complexes (Fricke et al., 2013a). Overall, these experiments will sort out the role of loop flexibility in acceleration of uncoating.

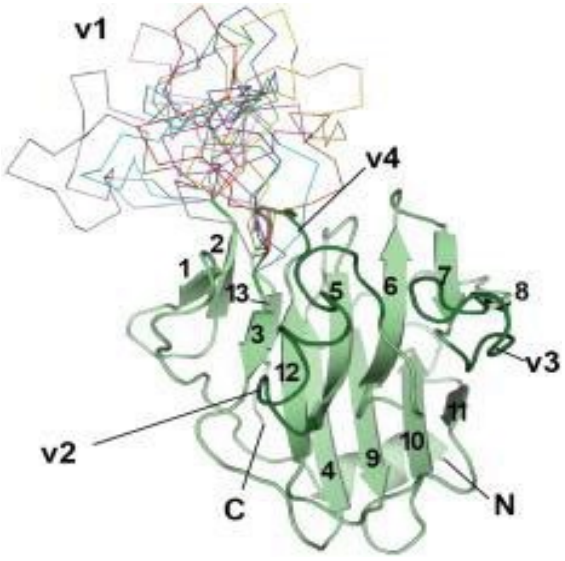

Figure 3. Structure of the PRYSPRY domain of rhesus monkey TRIM5α. The structure of the PRYSPRY domain is shown. The four variable loops of the protein are indicated as V1, V2, V3 and V4. The V1 loop, which directly interact with the HIV-1 core, exhibited hundred of different conformations, as indicated by the strands in different colors. These observations suggested that the PRYSPRY domain of TRIM5α exhibit great plasticity, which might allow the binding to different epitopes on the surface of the HIV-1 core. In addition, the movement of the V1 loop might be the energy necessary for accelerating the uncoating process of HIV-1.

3) MxB/Mx2

The restriction factor MxB is an interferon-a inducible protein that blocks HIV-1 infection in T cells (Goujon et al., 2013; Kane et al., 2013; Liu et al., 2013). Our investigations revealed that MxB blocks HIV-1 infection by inhibiting the uncoating process of HIV-1(Fricke et al., 2014) (Fig. 4). We found that MxB directly interacts with the HIV-1 core by using a triple arginine in the N-terminal domain of MxB (Schulte et al., 2015). Our studies also showed that oligomerization of MxB is essential for the ability of MxB to bind to the HIV-1 core and restrict HIV-1(Buffone et al., 2015). Overall, these results suggested that MxB binding to the core is forming an array on the surface of the HIV-1 core. Future experiments will test the hypothesis that MxB forms an array of protein on the surface of the HIV-1 core, which leads to inhibition of uncoating. To this end, we will perform Electron Microscopy of pure MxB protein overlaid on in vitro assembled HIV-1 CA that forms flat sheets. These experiments will show whether MxB cages the HIV-1 core in order to prevent HIV-1 uncoating. We are currently testing our purified MxB protein from human cells for its ability to interact with HIV-1 cores.

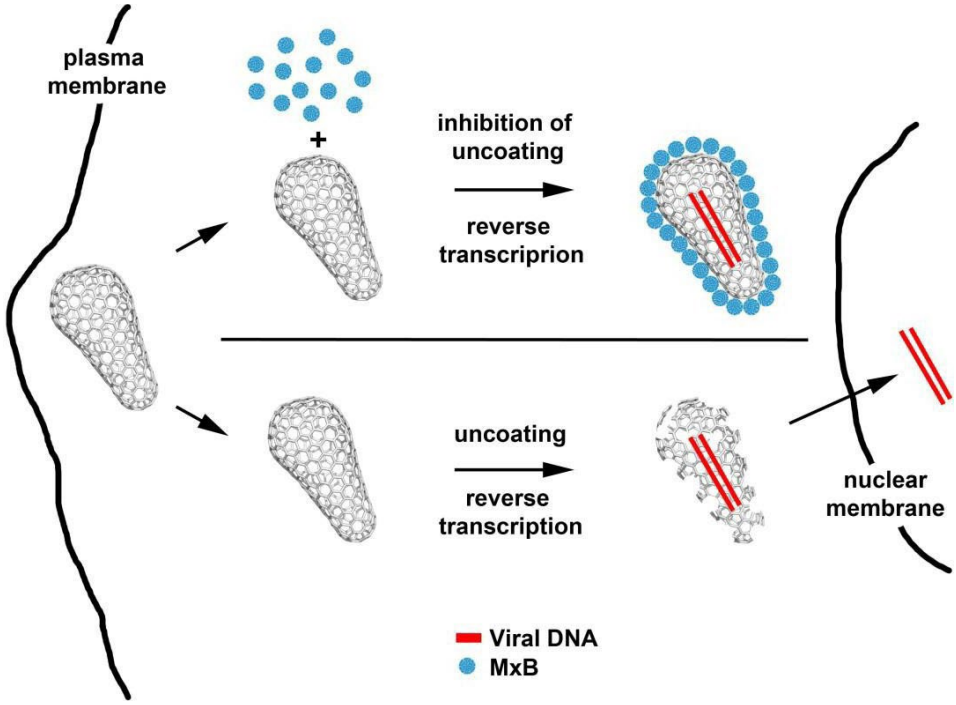

Figure 4. Inhibition of HIV-1 by MxB/Mx2. Our investigations revealed that MxB directly interacts with the HIV-1 core and prevents the uncoating process of HIV-1 terminating infection.

4) SAMHD1

The restriction factor SAMHD1 prevents HIV-1 infection of macrophages, dendritic cells, and resting T cells (Baldauf et al., 2012; Hrecka et al., 2011; Laguette et al., 2011). Our investigations revealed that SAMHD1 is regulated by phosphorylation of T592(White et al., 2013a; 2013b) (Fig. 5). The unphosphorylated form of SAMHD1 potently blocks HIV-1 infection. By contrast the phosphorylated form does not affect HIV-1 infection. These investigations suggested that the ability of SAMHD1 to block HIV-1 infection can be modulated. To this end, we are currently investigating in human primary cells the regulation of phosphorylation by different cytokines. We recently found that SAMHD1 is S-glutathionylated, and that this post- translational modification is essential for the ability of SAMHD1 to block HIV-1 infection. We are currently investigating the contribution of SAMHD1 S-glutathionylation to restriction. Although we have performed extensive biochemical and cellular characterization of SAMHD1(Brandariz- Nuñez et al., 2013; 2012; Ryoo et al., 2014; St Gelais et al., 2014; Welbourn et al., 2012; White et al., 2013b; 2014), we have not explored the role of SAMHD1 in immunity. Efficient lentiviral infection of macrophages in old world monkeys correlates with a strong adaptive immunity (Schaller et al., 2012).

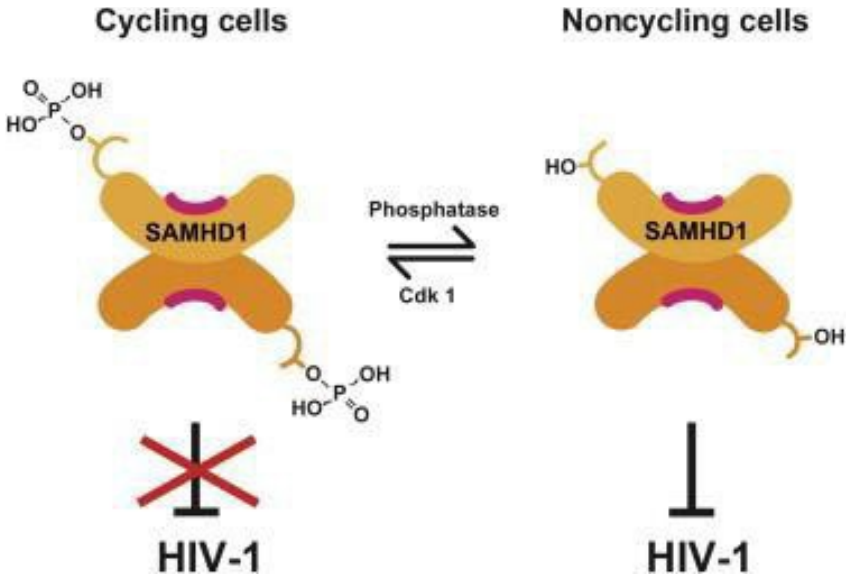

Figure 5. Regulation of SAMHD1 anti-HIV-1 activity by phosphorylation. Our investigations revealed that phosphorylation of SAMHD1 at T592 modulates the ability of this restriction factor to block HIV-1 infection of macrophages.

We are currently testing the hypothesis that SAMHD1 is involved in adaptive immunity. To this end, we will study adaptive immunity in the SAMHD1 knockout mice by testing antibody response, and the ability of the mice to prevent the growth of diverse pathogens. We will initially test pathogens that are known to be inhibited by SAMHD1, such as HSV-1/2(Kim et al., 2013) and mycobacterium tuberculosis (our unpublished preliminary studies). These investigations will help us understand the role of SAMHD1 in the immune system.

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(h-index=27, total citation=2618). Total papers = 69

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DR. TERESA DiLORENZO

Type 1 diabetes is an organ-specific autoimmune disease characterized by T cell-mediated destruction of the insulin-producing beta cells of the pancreatic islets. While insulin therapy allows for continuation of life, it neither cures the disease nor prevents its devastating complications. Studies utilizing the nonobese diabetic (NOD) mouse model of the disease have shown that T cells, recognizing autoantigenic peptides bound to major histocompatibility complex (MHC) molecules, are absolutely required for disease development. T cells specific for beta cell antigens can also be detected in the peripheral blood and islets of type 1 diabetes patients. Our laboratory utilizes a combination of *in vitro* and *in vivo* models and structural biology approaches to investigate the antigenic specificities, pathogenicity, and immunobiology of T cells in type 1 diabetes. Increasingly humanized models are continually in development in our group, and these are being used to develop and optimize antigen-specific therapeutic strategies. The goals of our work are to better understand the underlying immunopathogenesis of type 1 diabetes and to develop improved tools to monitor and manipulate pathogenic beta cell-specific T cells.

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Amdare, N. P., L. D. Shultz, D. L. Greiner, and **T. P. DiLorenzo**. 2024. Human insulin as both antigen and protector in type 1 diabetes. Eur. J. Immunol., doi: 10.1002/eji.202350949.

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DR. JOEL FRIEDMAN

Nanotechnology and Translational Research

We have developed a novel nanoparticle platform for topical and systemic drug delivery. The platform is capable of sustained delivery of therapeutic levels of nitric oxide. The high collaborative research program consists of nanoparticle platform development, platform characterization, preclinical applications including wound healing, antimicrobial therapies (MRSA, TB, Malaria), topical treatment of erectile dysfunction, hypertension and peripheral vascular disease, enhanced MRI imaging and targeted drug delivery. The goal is tissue specific drug delivery with imaging capability.

Protein Dynamics, Reactivity, Osmolytes and Solvent Slaving

We seek to understand how solvent motions modulate functionally important protein dynamics. Our approach focuses on the water surrounding the protein, the different categories of protein dynamics that contribute to functionality and how the interplay between water and protein dynamics is modulated by osmolytes.

Hemoglobin based blood substitutes and the role of NO/nitrite in the control of vasoactivity.

Dr. Friedman is the Director of the Einstein Blood Substitute Program Project which seeks through a multidisciplinary effort to create acellular hemoglobin-based blood substitutes for clinical use. A major focus is on the biophysical mechanisms through which hemoglobin in the presence of nitrite can generate stable nitrosothiols that cause vasodilation.

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DR. REBUMA FIRDESSA FITE

Area of Research: ***Nanomedicine and precision medicine approaches to better understand the pathophysiology of type 1 diabetes (T1D) and develop an effective antigen-specific immunotherapy***.

Studies show that the interactions between autoreactive T cells and β cell-derived peptides bound to major histocompatibility complex (pMHC) molecules are required to trigger the development of type 1 diabetes (T1D). However, autoreactive T cells have extremely lower reactivity to their cognate antigens as compared to non-self-reactive T cells, but how they are still able to elicit autoimmune responses and mediate β cell damage is yet to be elucidated. Moreover, a fundamental question, what controls the T cell receptor (TCR)-pMHC tri-molecular complex interaction to productively stimulate a T cell and direct an antigen-specific T cell response in a certain direction is not well known and it may hold a key to block T1D development. Dr. Fite is interested in addressing the above immunological questions by applying nanomedicine and precision medicine concepts. His NanoImmunology laboratory research interests revolve around the following three interrelated basic and translational research areas.

1. Understanding the pMHC-TCR binding properties and modulate for effective immunotherapy.
Post-translational modifications of native antigens and multiple other mechanisms produce neoantigens with altered physicochemical properties from their native forms. T cells responding to these modified epitopes increase as the disease advances and play a key role in the development of T1D. We are keen to understand how change in the physicochemical nature of antigenic peptides and the microenvironment of pMHC-TCR interactions would influence T cell fate and TCR repertoire, impacting T1D.

2. Discovering novel nanodelivery modalities for antigens.
Nanomaterials are instrumental in designing antigen-specific immunotherapy that incorporates various components targeted to different pathways. In collaboration with Berkland Lab at Washington University, we recently used a soluble antigen array (SAgA) that carries multiple copies of antigenic peptides bound to hyaluronic acid polymer and showed that SAgAs, but not free peptides, efficiently block the development of T1D in non-obese diabetic (NOD) mice at equivalent doses. Corroborating the result, the phenotypes of antigen-specific T cells induced by SAgA and the free peptides were also distinct, uncovering the critical role of the nanodelivery modalities to achieve therapeutic efficacy. Our goal is to develop a next generation nanodelivery platform that encompasses an antigen-specific component and alteration of the inflammatory microenvironment of islets to achieve lasting immune tolerance in T1D.

3. Developing human immune system (HIS) mouse models for T1D.
From a translational and practical standpoint, HIS mouse models offer an excellent opportunity to study human immune cells in vivo. The mice used for HIS models have combinations of mutations that make them extremely immunodeficient and allow the engraftment of human CD34+ hematopoietic stem cells. However, the currently available HIS mice still have several limitations. They lack well-developed lymphoid tissues, which are critical for the initiation and coordination of immune responses and develop a poorly understood condition with features of autoimmunity and graft-versus-host disease. Therefore, we are interested in developing improved HIS mouse models that recapitulate human physiology to better understand the pathophysiology of T1D and predict human immune responses to immunotherapy.

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DR. DAVID FOOKSMAN

The goals of my laboratory are to understand the regulation of plasma cell differentiation, migration, survival and function. Plasma cells are terminally-differentiated B cells that secrete high-affinity antibodies constitutively, following immunization and exposure to a pathogen. The quality, magnitude and longevity of the antibody response are dependent upon the differentiation and survival of these cells, which involves many signaling factors and auxiliary cell types. We have used intravital two-photon imaging to study plasma cell differentiation and migration in the lymph node and have found that that these cells exhibit a highly linear migration that is independent of $g_{\alpha i}$ chemotaxis. This migration is unique among lymphocytes and enables these cells to travel long distances crossing heterogeneous microenvironments to reach niches critical for their survival. In some cases, plasma cells may undergo malignant transformation during differentiation leading to neoplasms in humans such as multiple myeloma. Despite their critical role in immune function and disease, many fundamental questions remain regarding the physiology of plasma cells in vivo. We are using two-photon intravital imaging in combination with modern cellular and immunological tools to visualize and better understand the physiology of these cells under normal and pathological conditions. The current topics in the laboratory are focused on:

1. Plasma cell differentiation. What factors regulate selection and differentiation of germinal center B cells to plasma cell?
2. What factors control plasma cell migration to the bone marrow and subsequent long-lived survival and retention?
3. What factors control myeloma cell retention and migration in the bone marrow, which enables tumor progression?

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(* corresponding author, # senior author)

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DR. NIKOLAOS FRANGOGIANNIS

Our laboratory studies the cell biological mechanisms and the molecular signals involved in cardiac repair, remodeling and fibrosis. The adult mammalian heart has negligible regenerative capacity and heals through formation of a collagen-based scar. Repair of the infarcted heart is dependent on induction and timely suppression of inflammatory signals, and on recruitment of reparative cells (fibroblasts and vascular cells). Dysregulation of the inflammatory and fibrotic responses causes adverse remodeling of the heart and results in heart failure. Using cell-specific genetic manipulations, established mouse models of cardiac injury and remodeling, and cell biological assays (using isolated cardiomyocytes, fibroblasts and macrophages), we explore the molecular circuitry of myocardial repair and fibrosis. Ongoing studies address the following questions:

1. What are the signals implicated in suppression and resolution of the post-infarction inflammatory reaction?

Timely inhibition and spatial containment of inflammatory signaling are critical for cardiac repair. We study the role of macrophage-specific inhibitory signals in suppression and resolution of the post-infarction inflammatory reaction.

2. Which molecular pathways are responsible for fibroblast activation and de-activation in infarcted and remodeling hearts?

In the infarcted heart, fibroblasts critically regulate cardiac repair by transdifferentiating into myofibroblasts and by producing extracellular matrix proteins. However, excessive or dysregulated activation of fibroblasts results in extension of fibrosis and causes diastolic ventricular dysfunction. We study the molecular signals that activate and de-activate fibroblasts in cardiac repair, focusing primarily on the role and regulation of the TGF-beta cascade.

3. How does the extracellular matrix modulate the phenotype of cells involved in repair and fibrosis?

The extracellular matrix is not simply a structural scaffold, but actively participates in transduction of signaling responses. Specialized components of the matrix are induced following injury and modulate cytokine and growth factor-mediated responses, signaling through integrins or syndecan receptors. Our lab is particularly interested in the biology of these “matricellular proteins” in cardiac repair and remodeling.

4. How does metabolic disease cause cardiac fibrosis?

Diabetes and obesity are associated with profound alterations in cardiac function causing diastolic heart failure. Our lab studies the effects of metabolic dysregulation on cardiac fibroblasts and explores the mechanisms of fibrosis and capillary rarefaction in diabetic hearts.

5. What is the fate and role of pericytes in the infarcted and remodeling heart?

Pericytes are abundant in the mammalian heart and may regulate angiogenic and fibrogenic responses. Our lab studies the fate and role of pericytes in myocardial infarction.

The ultimate goal of our research is to identify therapeutic targets for attenuation of adverse remodeling following cardiac injury, thus preventing the development of heart failure.

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DR. VICTORIA FREEDMAN

DR. DAVID GOLDMAN

The medical community has long recognized fungi as important allergens for patients with asthma. Interestingly, fungal sensitization is more common in children and has been linked to severe asthma resulting in death. The accepted paradigm is that fungal sensitization occurs as a result of recurrent, transient environmental exposures. Yet, increasing evidence suggests that fungi may interact with people in unrecognized ways to promote asthma. My lab is interested in understanding the role of subclinical fungal infections in asthma and their potential contribution to the high prevalence of asthma in urban areas.

We have demonstrated that the majority of Bronx children older than 2 years have serologic evidence of cryptococcal infection. *Cryptococcus neoformans* is an encapsulated fungus that is well suited to serve as co-factor in urban asthma. *C. neoformans* colonizes pigeon droppings and is endemic to urban areas. Once inhaled, this fungus causes persistent, subclinical infections. Cryptococcal infection induces TH2 inflammation in animal models. In a rat model, we have shown that cryptococcal pulmonary infection acts a co-factor to enhance allergic inflammation to allergen challenge and promotes airway hyper-responsiveness, both hallmark features of asthma. Pulmonary cryptococcosis also induces chitinase expression, which has recently been implicated as an essential mediator of allergic inflammation.

In addition to fungal studies, my lab is interested in anthrax pathogenesis. *Bacillus anthracis* is widely recognized as a potential agent of bioterrorism as evidenced by the 2001 anthrax attack. The toxins of *B. anthracis* are essential to virulence. In collaborations with Drs. Arturo Casadevall and Jurgen Brojatsch, we have studied the mechanisms by which *Bacillus anthracis* toxins contribute to host death. We have identified a previously unrecognized protease in human serum that inactivates the protective antigen component of lethal toxin *in vitro*. The precise protease and its role in the host response and susceptibility to anthrax remain to be determined. We have also identified a potential role for platelet activating factor (PAF) in mediating the lethal effects of toxin, including the alterations in vascular permeability which is characteristic of anthrax. Together, these observations may have important implications in developing new approaches to the treatment of anthrax.

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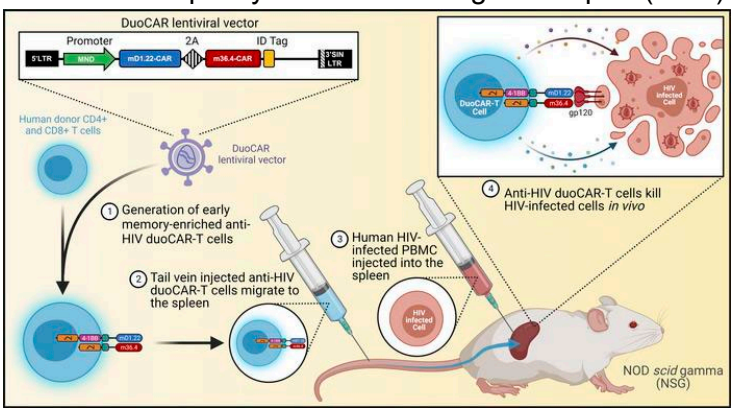
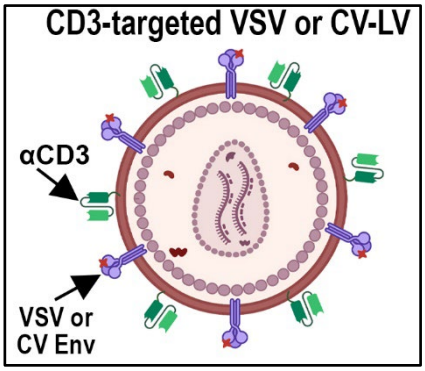
DR. HARRIS GOLDSTEIN

Our laboratory is utilizing novel molecular, cellular and biochemical approaches to weaponize the immune system by using an artificial immunity (AI) strategy to boost immune response to treat infectious diseases and cancer. One strategy we are utilizing is to develop novel CAR-T cells for infusion into people living with HIV (PLWH) which can control HIV infection by efficiently eliminating HIV-infected cells. The development of combinational antiretroviral therapy (ART) which targets different steps in the HIV replication cycle has enabled long-term survival of PLWH. However, despite long-term reduction of HIV to undetectable levels, resurgence of viremia occurs soon after the cessation of ART demonstrating that years of successful suppression of active viral replication did not cure HIV infection. HIV cure was prevented by the presence of HIV reservoirs consisting of latent HIV-infected cells distributed throughout the body, which survive despite standard or intensified ART and can produce infectious virus and reintroduce HIV infection after the cessation of ART. Nevertheless, HIV has been cured in a few PLWH after transplantation of allogeneic hematopoietic stem cells from donors whose T cells are resistant to HIV infection due to a homozygous mutation in the HIV coreceptor, CCR5. This breakthrough demonstrated that HIV could be cured. However, the high morbidity and mortality associated with bone marrow transplantation limits the routine application of this approach and provides a strong rationale for pursuing alternative strategies for providing ART-free HIV remission by leveraging observations that potent HIV-specific immune responses could provide sustained ART-free remission in PLWH.



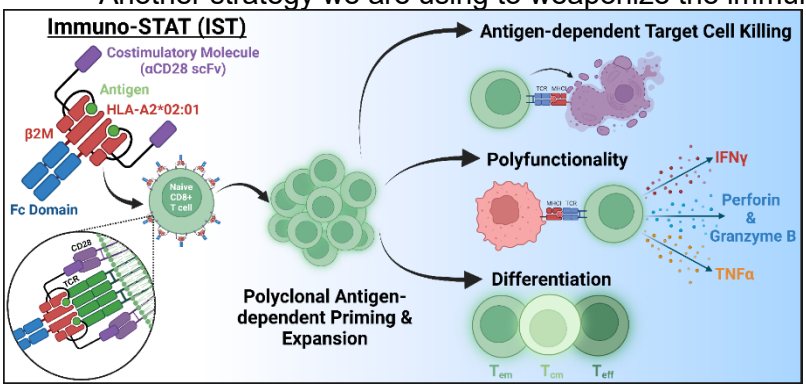
The capacity of chimeric antigen receptor (CAR)-T cells engineered to target malignant cells to induce remission and cure in cancer patients made this an attractive approach to provide PLWH with a potent HIV-specific immune response. Our lab has collaborated with the Caring Cross group to develop, optimize and validate the duo-CAR architecture which co-express two independent CARs (duoCAR-T cells), each recognizing a different gp120 epitope and linked to a different costimulatory signaling domain. We demonstrated that this architecture which targets two highly conserved gp120 epitopes, the CD4 binding site for the HIV gp120 envelope and the HIV co-receptor binding region, enables duoCAR-T cells to be extremely resistant to HIV infection and markedly inhibit in vivo HIV infection by a broad range of variants, which should deter HIV immune escape. After validating the in vitro efficacy of these duoCAR-T cells in tissue culture, we used a humanized mouse model we developed that supports HIV infection to demonstrate the in vivo ability of the duoCAR-T cells to control HIV infection. This data was crucial for supporting the approval of this treatment by the FDA for advancement into clinical trials. The duoCAR-T-cell therapy is currently being evaluated in an ongoing phase I/IIa clinical trial with PLWH (NCT04648046). We are currently developing the next generation of duoCAR-T cells which display increased potency and persistence. In addition, we are developing a new generation of CAR-T cells that we engineered by transduction with antibody-encoding lentiviral gene vectors (LV) enabling T cells which confer them with the ability to produce broadly neutralizing antibodies capable of potently suppressing HIV infection. These CAR-T-B cells can deliver a one-two punch to control HIV infection by not only killing cells already infected with HIV, but also preventing the further spread of infection.

However, even if duoCAR-T cell or duoCAR-T-B cell treatment would provide a functional HIV cure for the estimated 40 million PLWH worldwide, the high manufacturing costs and complex infrastructure required for laboratory production of CAR-T cells followed by reinfusion into patients limits its wider use for HIV treatment in low- and middle-income countries, where HIV infection is most prevalent. To overcome this barrier to wider application of CAR-T cells therapies for HIV as well as for cancer, we are developing a lower-cost and highly scalable T cell-targeted lentiviral delivery technology for producing HIV-specific CAR-T cells in patients' bodies rather than in highly specialized laboratories. For this purpose, we are designing, optimizing and evaluating LV containing an anti-CD3 scFv anchored in the lentiviral membrane, to specifically bind and transduce T cells in vivo and engineering them into duoCAR-T and/or duoCAR-T-B cells. Expression of an anti-CD3 scFv on the lentiviral surface will have two functions. It will enable the LV to activate the T cell to permit it to be



effectively transduced while also adding in vivo cellular selectively to T cells, the transduction target. If successful, this strategy will provide a highly scalable approach to provide PLWH sustained and robust anti-HIV CAR-T cell and antibody responses which will enable them to achieve sustained ART-free remission.

Another strategy we are using to weaponize the immune system is a modular biologic platform termed



Immuno-STAT (IST), that selectively expands antigen-specific T cells by delivering antigen-specific TCR and co-stimulatory signals through HLA-A2 MHC molecules covalently-tethered to pathogen-derived peptides (pMHC) and linked CD28- or 4-1BB-specific ligands, respectively. These biologics were developed by the Almo lab and immunologically and functionally validated by our lab as an immunotherapeutic for the in vivo expansion of antigen-specific CTL to eliminate virally infected or cancerous cells. The immune response of naïve CD8+ T cells is initiated by three coordinated signals delivered by antigen-presenting cells: Signal 1 delivered by engagement between antigen-specific TCR and its cognate peptide-MHC complex (pMHC); Signal 2 provided by co-stimulatory receptors, such as CD28 and 4-1BB, through interactions with the B7 and 4-1BBL ligands, respectively; and Signal 3 supplied by cytokines, such as IL-7, IL-21, IL-2, or IL-15, which modulate cellular proliferation and differentiation. We demonstrated that ISTs carrying a pMHC alone, a pMHC linked to a CD28 agonist, or pMHC linked to a 4-1BB agonist were all able to induce activation and selective expansion of cytotoxic virus-specific memory CD8+ T cells in vitro and to potently suppressed in vitro and in vivo HIV and CMV infection.

In addition to using these IST as an immunotherapeutic, we are also using them to delineate the minimum signals required to activate and expand antigen-specific memory CD8+ T cells because they can specifically deliver a T cell receptor (TCR) signal alone or paired with a defined co-stimulatory signal to naïve and memory antigen-specific CD8+ T cells. Using a reductionist approach that provides defined TCR and co-stimulatory signaling, we demonstrated that different IST could engage TCR alone or in combination with either CD28 or 4-1BB costimulatory to initiate distinct transcriptional programs in memory CMV-specific CD8+ T cells. As compared to activation by TCR signaling alone, the combination of TCR and CD28 or 4-1BB co-stimulatory signals significantly altered the transcriptome and drove expression of genes related to growth and survival. Nevertheless, TCR signaling alone was sufficient for robust recall activation and expansion of functional cytomegalovirus CMV-specific and HIV-specific memory CD8+ T cells. This response contrasts with naïve CD8+ T cells, which required CD28 co-stimulation in addition to TCR stimulation for antigen-specific activation. These results have important implications for antigen-specific immunotherapy by indicating that biologics that deliver TCR signals alone may be sufficient for immunotherapeutic strategies designed to expand memory CD8+ T cells to eliminate cancerous or infected cells. However, strategies that aim to stimulate naïve T cell responses would require the codelivery of TCR and CD28 signals.

We leveraged these findings to applying the IST for developing a new strategy for expanding antigen-specific CD8+ T cells to enable them to be used for adoptive cell transfer (ACT), a promising and rapidly developing immunotherapeutic approach to treat cancer which holds considerable potential as an therapeutic strategy to reconstitute the anti-viral immunity in immune-compromised patients to prevent their development of life-threatening viral infections. We demonstrated that the capacity of this IST platform to deliver TCR and CD28 signals to activate and generate large numbers of highly functional cytotoxic CD8+ T cells from the naïve repertoire specific for the melanoma-associated MART-1 antigen and the HIV-associated SL9 antigen. In contrast to naïve MART-1-specific CD8+ T cells which could be activated by both MART-1-peptide loaded dendritic cells and MART-1-specific IST, naïve SL-9-specific CD8+ T cells could be activated by SL9-specific IST but not by SL9-peptide loaded dendritic cells. This innovative approach has the potential to streamline the expansion of de novo antigen-specific T cells, overcoming the logistical hurdles limiting the wider use of ACT and enhancing its effectiveness as a therapeutic strategy for both cancer and HIV.

PUBLICATIONS: (Graduate student and MSTP student authors are indicated by underlining)

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DR. CLAUDIA GRAVEKAMP

Our laboratory is focused on the development and testing of cancer immunotherapy and non-immune-based cancer therapies. Since most cancer deaths occur by metastases (primary tumors can often be removed by surgery, chemotherapy, or radiation), our therapies are focused on the treatment of metastases. We have developed various therapies using different novel approaches, in preclinical mouse tumor models with metastatic breast and pancreatic cancer. For instance, we use an attenuated bacterium *Listeria monocytogenes* as a platform for the delivery of anticancer agents to the tumor microenvironment and into tumor cells such as radioactivity, tumor-associated antigens, or small molecules like alphagalactosylceramide, or we kill tumor cells through cryoablation by freezing and thawing tumor cells, combined with various adjuvants targeting myeloid-derived suppressor cells (MDSC) such as stimulator of interferon genes (STING)-ligand cyclic di-guanylate (c-di-GMP, Curcumin, and AMD3100. Since MDSC play a major role in immune suppression in the tumor microenvironment, MDSC are an important target in cancer immunotherapies. We also focus on the age factor since most cancer patients are old and elderly react less efficient to vaccines than young adults. The MDSC are present in blood of patients and mice with cancer. This MDSC population is strongly increased in the tumor microenvironment particularly at older age and contributes to the age-related T cell unresponsiveness. We also developed a combination therapy with gemcitabine and nicotinamide that reduces the stromal barrier in pancreatic tumors and attract and activated T cells to the tumors and metastases, resulting in a strong reduction of advanced pancreatic cancer. This was published in JITC in 2020. Based on this study we started collaborating with clinicians at Montefiore who became interested in the therapy (Dr. Ana Acuna-Villaorduna). They are now preparing for a clinical trial with gemcitabine and nicotinamide in pancreatic cancer patients at Montefiore and Mount Sinai.

Recently, we developed a unique cancer immune therapeutic approach that takes immunosenescence and lack of neoantigen expression into account. Using an attenuated bacterium, *Listeria monocytogenes* (Listeria), we can deliver so-called recall antigens (Listeria-RA), directly into tumor cells with high efficiency through in vivo infection. Recall antigens are highly immunogenic antigens to which the cancer patient has been exposed early in life, such as tetanus toxoid (TT), measlevirus (MV) and poliovirus (PV). They function as a neoantigen surrogate. Virtually all individuals have nowadays been vaccinated against such diseases resulting in memory T cells, circulating in blood for life, that can be reactivated by Listeria-RA at any time, even at old age, and then kill the Listeria-RA-infected tumor cells. So, even if in an aged cancer patient there are no longer well-functioning T cells, the existing memory T cells can still mount a very powerful immune response. This approach avoids the need of naïve T cells during treatment at older age. We published this work in *Sci Transl Med* in 2022. We are preparing for a Phase I clinical trial in patients with advanced pancreatic cancer in collaboration with Drs. Chaoyuan Kuang and John McAuliffe of Montefiore Einstein Medical Center. Loki Therapeutics, a start-up company in New York City has raised funding for the clinical trial.

Listeria-based cancer vaccines

Attenuated *Listeria monocytogenes* is a weakened facultative anaerobic bacterium (non-toxic and non-pathogenic) and has been used to deliver antigens into antigen-presenting cells. We developed various Listeria-based constructs expressing tumor-associated antigens including Mage-b, Survivin, p53 etc and tested these constructs in mice with metastatic breast and pancreatic cancer and demonstrated a significant reduction in metastases and tumor growth. In addition, we have further improved the efficacy of the Listeria-Mage-b vaccine with help of MDSC-targeting adjuvants like c-di-GMP and Curcumin. However, in 2009 our lab discovered that Listeria infects and kills tumor cells by the generation of reactive oxygen species (ROS) through the activation of the NADPH-oxidase pathway and left healthy tissues unharmed. Based on this tropism for the tumor microenvironment we started using Listeria as a platform for the selective

delivery of anti-cancer agents to the tumor microenvironment. For more detail see Kim et al, Cancer Res 2009; Chandra et al, Cancer Immunology Research, 2014.

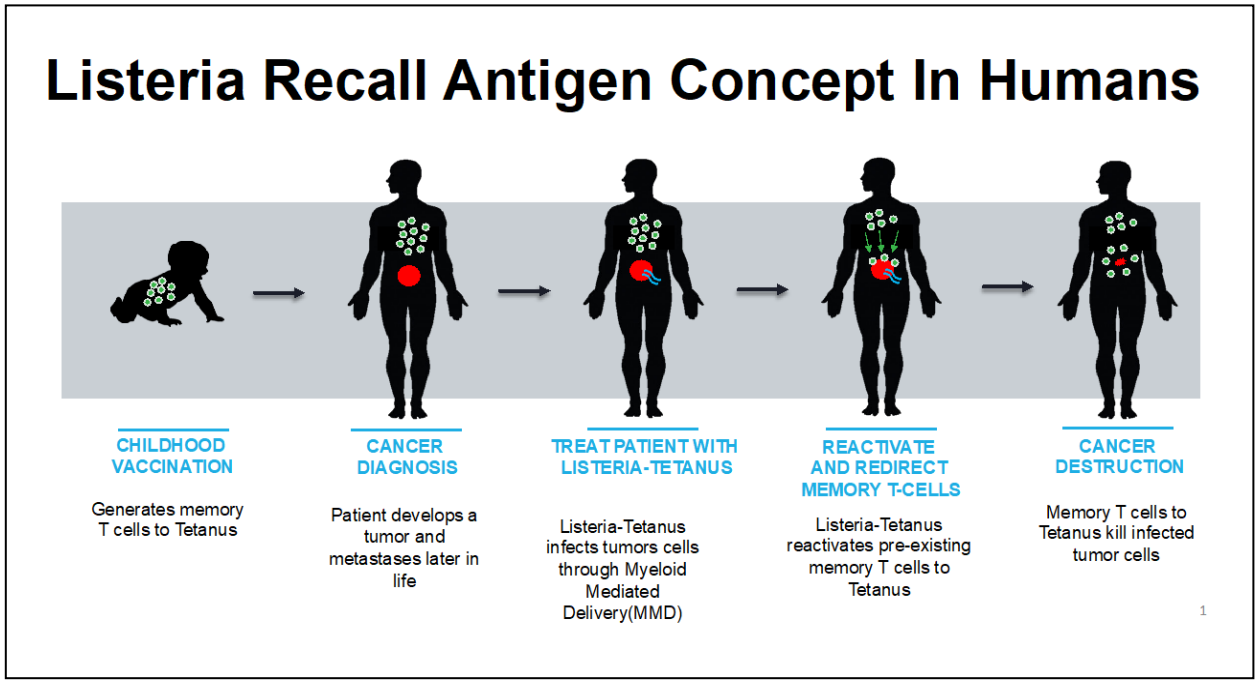
Mechanisms that contribute to the selective survival and multiplication of Listeria in the tumor microenvironment

We have analyzed potential mechanisms explaining why Listeria survived and multiplied in the TME and not in healthy tissues. We discovered that Listeria is protected from immune clearance in the TME through strong immune suppression, but is rapidly killed in healthy tissues that lack immune suppression. In addition, we found that MDSC play an important role in the selective delivery and survival of Listeria in the tumor microenvironment. MDSC are selectively attracted by the primary tumor through the production of attractants such as granulocyte macrophage-colony stimulating factor (GM-CSF), interleukin (IL)-6, A100. Listeria infects, survives and multiplies in MDSC of tumor-bearing mice, and is protected from immune clearance because of the immune suppressive character of MDSC. We have shown that Listeria, once at the tumor site, infects (and kills) tumor cells directly or spreads from MDSC into tumor cells through the cell-to- cell spread mechanism specific for Listeria. For more detail see Quispe-Tintaya et al, PNAS 2013**;** Chandra et al, BJC, 2013.

Radioactive Listeria for the treatment of pancreatic cancer

Ninety six percent of patients diagnosed with pancreatic cancer have only 6 months to live, despite aggressive treatments. This underlines the urgent need for new effective therapies. In collaboration with Dr. Ekaterina Dadachova (Department of Radiation, Einstein), we developed a radioactive Listeria for the treatment of pancreatic cancer, by coupling ^{188}Rhenium to anti-Listeria antibodies followed by incubation with Listeria bacteria. This resulted in the synergistic destruction of cancer cells through Listeria-induced ROS and through ionizing radiation of the ^{188}Re. The number of metastases was reduced by 50% in mice treated with Listeria alone, and by 90% in mice treated with Listeria-^{188}Re. This correlated with the accumulation of radioactivity in the metastases. This was the first time that a live attenuated bacterium was successfully used to deliver radioactivity selectively to the tumor microenvironment. The potential of the radioactive Listeria for the treatment of pancreatic cancer was discussed in several high profile journals like Science, Nature, as well as lay Journals like The Economist, Forbes Magazine and many others. Currently, we are testing Listeria with other radioisotopes. For more detail see Quispe-Tintaya et al, PNAS 2013. Recently, we developed Listeria-32P by incorporating 32P-phosphorus directly into the Listeria during culture. Most likely of the longer half-life of 32P (14 days) than of 188Rhenium (16.9 hrs), Listeria-32P was also highly effective against tumors and metastases in syngeneic and transgenic mouse models of pancreatic cancer. For more detail see Oncotarget 2017.

Listeria-recall antigens



Concept in humans. *Childhood vaccinations with tetanus toxoid (TT) generate TT-specific memory T cells, which circulate in the blood for life. After appearance of pancreatic cancer (late in life), the patients will receive one high dose with Listeria-TT to deliver TT into tumor cells, followed by multiple low doses of Listeria-TT over a period of 2 weeks to stimulate the pre-existing memory T cells to TT. MDSC are involved in the delivery of Listeria-TT to the TME. Reactivated memory T cells will in turn destroy the tumor cells expressing TT. Multiple low doses of GEM will be added after TT has been delivered at the tumor site, which reduce immune suppression by eliminating MDSC and TAM (not shown here).*

Listeria incorporated with alphagalactosylceramide

In collaboration with Dr. Steven Porcelli (Department Microbiology and Immunology, Einstein), we incorporated alphagalactosylceramide (αGC) into the Listeria bacteria simply during culture. This method was originally developed for mycobacteria. αGC is a marine sponge that activates natural killer T cells (NKT) cells, which in turn stimulates other immune cells like natural killer (NK) cells and T cells. We demonstrated that Listeria expressing tumor-associated antigen Mage-b incorporated with αGC created an immune-stimulating environment that attracted the NKT cells to the metastases, resulting in improved activation of CD8 T cells to Mage-b and a dramatic reduction in the number of metastases in a mouse model of metastatic breast cancer (4T1). For more detail see Singh et al, BJC 2014.

Cryoablation combined with adjuvants

Cryoablation involves killing of tumor cells through freezing and thawing, resulting in recruitment of tumor-specific T cells. Since MDSC strongly inhibits these T cells we have the cryoablation combined with MDSC-targeting adjuvants like STING ligand c-di-GMP, Curcumin, and AMD3100. c-di-GMP reduces the number of MDSC and converts a subpopulation of MDSC into an immune- stimulating phenotype producing IL-12 (stimulates T cells). Curcumin reduces IL-6 produced by MDSC and breast tumors. IL-6 strongly inhibits T cells in the tumor microenvironment. AMD3100 is a small

molecule that prevents the interaction of CXCR4 on MDSC and stromal cell-derived factor (sdf-1) on tumor cells. Currently, these combination therapies are under investigation in mice with metastatic breast cancer in collaboration with the Anticancer Fund (Brussels, Belgium). Preliminary results are extremely promising. Cryoablation and Meriva (Curcumin derivate) significantly delayed the onset of metastases and eliminated completely the primary tumor, prolonged the survival rate compared to the control groups in correlation with improved CD8 T cell responses to multiple tumor-associated antigens. For more detail see Chandra et al, OnoImmunology 2015.

Feasibility of cancer vaccination at older age

Cancer is a disease of the elderly. When cancer becomes metastatic, it often needs aggressive second-line treatment, for which the options are limited. This is particularly challenging for frail, elderly cancer patients in which comorbidity plays an antagonistic role. Immunotherapy is the most promising and benign option for preventing or curing metastatic cancer in such patients. Unfortunately, cancer immunotherapy is less effective at old than at young age, due to T cell unresponsiveness, especially in the tumor microenvironment (TME). Various causes have been described for T cell unresponsiveness at old age, such as lack of naïve T cells at older age, deficiency in the upregulation of co-stimulatory molecules on aged dendritic cells (DCs), and most recently, the increase in the population of MDSC in the TME of old compared to young mice, among other age-related immune impairments. As mentioned above, Listeria has an intimate relationship with MDSC. We have shown that Listeria-based vaccination was equally effective in young and old mice with metastatic breast cancer by targeting MDSC. The Listeria killed the tumor cells directly through ROS, and Listeria-activated T cells killed the infected tumor cells presenting the Listeria antigens. For more detail see Chandra et al, BJC, 2013.

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RESEARCH IMPACT

Commentary on paper about Radioactive Listeria by Quipe-Tintaya et al. in PNAS 2013. Stritzker J, and Szalay AA. Single-agent combinatorial cancer therapy. www.pnas.org/cgi/doi/10.1073/pnas.1305832110.

Websites of Journals and magazines that discussed the impact of the radioactive Listeria for therapeutic treatment of pancreatic cancer:

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https://www.sciencenews.org/article/microbes-can-redeem-themselves-fight-disease

DR. LAWRENCE HERBST

Area of Research: ***Animal models of infectious disease; effects of adventitious infections on research; novel transforming viruses***

DR. BETSY HEROLD

Dr. Herold's lab focuses on 3 major areas of research. The first project focuses on defining molecular mechanisms that contribute to the **HIV-HSV syndemic** and translating these findings into the clinic with the goal of developing novel therapeutic or prevention modalities. Recently, in work spearheaded by a graduate student, they showed that HSV infects CD4+ T cells and induces transcriptional and epigenetic changes in the infected and bystander cells that promote HIV reactivation and replication. (ii) The second major focus is the **development of vaccines and monoclonal antibodies (mAbs) for the prevention and/or treatment of herpes simplex viral infections (HSV).** In collaboration with William Jacobs, PhD, the lab engineered a single-cycle HSV-2 virus deleted in the essential envelope glycoprotein D (gD), as part of their studies of viral entry. Serendipitously, they found that this deletion virus elicits high titer, polyantigenic and polyfunctional antibodies that provide complete protection in male and female mice against clinical isolates of HSV-1 and HSV-2. This vaccine is currently being advanced through nonclinical safety and manufacturing studies for future clinical trials. In addition to ongoing vaccine development work and isolation of protective mAbs, the lab is focused on mechanistic studies to determine why this vaccine elicits protective immune responses that differ from the response to acute infection (which does not protect against recurrences) and to other candidates that have failed in clinical trials. Primary infection and the other gD+ vaccines elicit a predominant neutralizing antibody response whereas the gD null virus elicits antibodies that primarily mediate antibody-dependent cell mediated cytotoxicity (ADCC). Ongoing work led by graduate students uncovered a novel immune evasion strategy that may explain our findings. Glycoprotein D binds to an immunomodulatory molecule, HVEM (TNRSF14) on immune cells, which is required for optimal generation of ADCC-mediating antibody responses. HVEM signaling also contributes to the ability of NK (and other effector cells) to activate Fcgamma receptor signaling that leads to killing of target cells. (iii) The third major project in the lab focuses on identifying the signaling pathways that **HSV usurps for entry**: Current work from the laboratory demonstrates that HSV activates phospholipid scramblase, which triggers the translocation of phosphatidylserines to the outer leaflet of the plasma membrane. Surprisingly, this also results in translocation of Akt to the outside where it becomes activated (phosphorylated) to promote viral entry. In collaboration with the Almo lab (Chair, Dept of Biochemistry), we have developed cell impermeable kinase inhibitors as tools to study this outside-inside signaling pathway. Results demonstrate that several viruses (including SARS-CoV-2) activate this pathway to promote viral entry. We are using these tool compounds to further define the signaling pathway and its role in viral entry and in cell biology. In addition to these basic research studies, the lab also leads or collaborates in translation studies on the vaginal microbiome and its link to HIV and STI risk as well as clinical studies in pediatric transplant recipients.

Representative publications are listed below (students/postdocs/mentored faculty are in bold).

PUBLICATIONS

1. **Pierce, C.A**., **Loh, L.N.,** Steach, H.R., Cheshenko, N.C., Preston-Hurlburt, P., Zhang, F., Stransky, S., **Kravets, L**., Sidoli, S., Philbrick, W.M., Nassar, M.N., Krishnaswamy, S., Herold, K.C.*, Herold, B.C.* (*contributed equally). HSV-2 triggers upregulation of *Malat1* in CD4+ T cells and promotes HIV latency reversal. *JCI*, 2023, June 1; 133(11):e16531 PMC10232005.

2. **Mahant, A.M., Gromisch, M.S., Kravets, L., Aschner, C.B**., and Herold, B.C. Greater durability and protection against herpes simplex viral disease following immunization of mice with single-cycle DgD-2 compared to an adjuvanted glycoprotein D protein vaccine. Vaccines, 2023 Aug 14; 11(8):1362 PMC10458853

3. **Mahant, A.M**, Estrada Trejo, F., Aguilan, J.T., Sidoli, S., Permar, S.R., and Herold, B.C. Antigenic target, glycans, affinity for and placental expression of Fc receptors modulate HSV IgG transfer. iScience, 2023 Aug 15; 26(9):107648 PMC10475509
4. **Cheshenko, N**. Bonanno, J.B., Hoffmann, H-H., Jangra, R.K., Chandran, K., Rice, C.M., Almo, S.C. and Herold, B.C. Cell-impermeable staurosporine analog targets extracellular kinases to inhibit HSV and SARS-CoV-2. *Nature Communications Biology*, 2022;5(1):1096. PMC9569420.

5. Kuraoka, M., **Burn Achner, C**., Windsor I.W., **Mahant, A.M**., Garforth, Sc., Kong, S.L., Achkar, J.M., Almo, S.C., Kelsoe, G., and Herold, B.C. A non-neutralizing glycoprotein B monoclonal antibody protects against herpes simplex virus disease in mice. *JCI* 2023 Feb 1;133(3):e161968 PMC9888390
6. **Mahant, A.M., Guerguis, S**., Blevins,T., **Cheshenko, N**., Gao, W., Anastos, K., Belshe, R. and Herold, B.C. Herpes Simplex Virus Glycoprotein D Antibodies Fail to Elicit Antibody-Dependent Cell-Mediated Cytotoxicity: Implications for Future Vaccines. *Journal of Infectious Diseases,* Nov 1;226(9):1489-1498 PMID:35834278
7. **Pierce CA, Sy S**, Galen B, Goldstein DY, Orner E, Keller M, Herold KC*, **Herold B.C*** (*****contributed equally**).** Natural mucosal barriers and COVID-19 in children. *JCI Insight* 2021.May10;6(9):e148694.PMC8262299
8. **Burn Aschner, C., Loh, L.N.,** Galen, B., Delwel, I., Jangra, R.K., Garforth, S.J., Chandran, K., Almo, S.C., Jacobs, W.R., Ware, C. F., and Herold, B.C. HVEM signaling promotes ADCC vaccine responses to herpes simplex viruses. *Science Immunology*, 2020, Aug 14;5(50): eaax2454. doi: 10.1126 PMC7673108
9. **Pierce, C.A**., Preston-Hurlburt, P, Dai, Y, **Burn Aschner, C., Cheshenko, N.,** Galen, B., Garforth, S.J., Herrera, N.G., Jangra, R.K., Morano, N., Orner, E., Sy, S., Chandran, K., Dziura, J., Almo, S.C. Ring, A., Keller, M.J., Herold, K.C*. and Herold, B.C*(*contributed equally). Immune responses to SARS-CoV-2 infection in hospitalized pediatric and adult patients. *Sci Transl Med* 2020 Sep 21;eabd5487do10.1126/ PMC7658796
10. **Taneva, E**., Sinclair, S., **Mesquita, P.M.M**., Weinrick, B., Cameron, S.A., Cheshenko, N., Reagle, K., Frank, B., Srinivasan, S., Fredricks, D., Keller, M.J. and Herold, B.C. Vaginal microbiome modulates topical antiretroviral drug pharmacokinetics. JCI Insight, 2018 Jul 12;3(13). pii: 99545. doi: 10.1172/jci.insight. 99545 PMC6124523
11. **Ramsey, N., Visciano, M., Hunte, R. Loh, L.N., Burn Aschner, C**., Jacobs, W.R., and Herold, B.C. A single-cycle glycoprotein D deletion viral vaccine candidate, delta gD-2, elicits polyfunctional antibodies that protect against ocular herpes simplex virus, Journal of Virology 2020 Jun 16;94(13):e00335-20. doi: 10.1128/JVI.00335-20. Print 2020 Jun 16 PMC7307146
12. **Cheshenko, N., Pierce, C**., and Herold, B.C. Herpes simplex viruses activate phospholipid scramblase to redistribute phosphatidylserines and Akt to the outer leaflet of the plasma membrane and promote viral entry. PLoS Pathog. 2018 Jan.2;14(1):e1006766 PMC5766253

DR. BENJAMIN HIMES

DR. ADILIA HORMIGO

DR. WILLIAM R. JACOBS JR.

Sterilizing Chemotherapies and Immunotherapies against Tuberculosis, Leprosy, Herpes, and Influenza

Tuberculosis and Leprosy – Slow-growing bacteria that survive sterilization by drugs and adaptive immunity

Tuberculosis (TB) and Leprosy are two diseases caused by the slow-growing mycobacteria, *Mycobacterium tuberculosis* and *Mycobacterium leprae*. Whereas the fast-growing *Mycobacterium*, *M. smegmatis* doubles every three hours, *M. tuberculosis* doubles every 18 to 24 hours, and *M. leprae* doubles every 14 days. Leprosy causes gross skin disease and nerve damage and still afflicts over 4 million people worldwide. TB is only second to COVID-19 in deaths for the last two years, but causes, on average over 1.3 millions deaths a year for the last 100 years. TB is called the forgotten pandemic that remains a global health problem despite the availability of a TB vaccine (BCG) and sterilizing chemotherapy. Why do these diseases remain significant global health problems? The answer is these bacteria share the evolved property that they can form persisters. Persisters are a subpopulation of cells that can survive sterilization in mammals. We hypothesize that both pathogens have evolved slow growth as a mechanism to escape killing assaults by bacteriocidal drugs or adaptive immune responses. Phenotypic tolerance of killing mechanisms are complex traits regulated transcriptionally and post-translationally. To gain knowledge of these complex phenotypes, we make mutants in *M. tuberculosis* with transposons or precise null bar-coded deletions. These genetic perturbations are delivered by mycobacteriohages, viruses that infect mycobacteria, which we have engineered to use as tools. In addition to *M. tuberculosis* studies, we are using mycobacteriophage based systems to engineer the leprosy bacillus to glow and grow to provide better models for discovering new therapeutics. Indeed, the leprosy bacillus has never been cultivated on artificial media. Genetic manipulation of these pathogenic mycobacteria, along with the use of genetically defined mouse mutants offer platforms of discovery to design new strategies to sterilize these organisms with drugs or adaptive immune responses.

Herpes and Influenza:
In collaboration with Dr. Betsy Herold, the Jacobs lab has generated a precise deletion of the gene encoding *gD* of Herpes Simplex Virus (HSV) 2, termed ΔgD-2, that upon immunization in mice elicits sterilizing immunity against challenge with HSV-1 and HSV-2. This unprecedented protection results from the induction of a special type of antibodies that mediate antibody dependent cell mediated killing (ADCK) of herpes infected cells. They have subsequently found that many pathogens do not elicit ADCK antibodies but they hypothesized that by cloning genes encoding important antigens into our herpes viral vector, they could elicit protection against other pathogens such as influenza. Recently, the Jacobs lab generated recombinant ΔgD-2 herpes virus expressing genes encoding flu antigens and demonstrated that we can confer complete protection against the homologous influenza challenge. This proof of principle suggests that by cloning antigens from other pathogens, such as *Mtb*, it is possible to make novel vaccines and elicit ADCK antibodies. Thus, other efforts in the Jacobs lab focus on characterizing the mechanisms by which ADCK antibodies facilitate the collaboration of innate immunity with adaptive immune responses.

Lab Website: http://williamrjacobs.org/

Select Publications:

Kaugars, K., Dardick, J., de Oliveira, A.P., Weiss, K., Lukose, R., Kim, J., Leung, L., Rajagopalan, S., Wolin, S., Akabas, L., Knipe, DM., Bajic, G., Jacobs, WR. A Recombinant Herpes Virus Expressing Influenza Hemagglutinin Confers Protection and Induces Antibody-Dependent Cellular Cytotoxicity. *Proc Natl Acad Sci U S A.* 2021

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Vilcheze, C., Hartman, T., Weinrick, B., Jain, P., Weisbrod, T.R., Leung, L.W., Freundlich, J.S. and Jacobs, W.R., Jr. (2017). Enhanced respiration prevents drug tolerance and drug resistance in Mycobacterium tuberculosis. *Proc Natl Acad Sci U S A.* 114(17):4495-4500. PMCID: PMC5410800

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Petro, C., González, P.A., Cheshenko, N., Jandl, T., Khajjoueinejad, N., Bénard, A., Sengupta, M., Herold, B.C., Jacobs, W.R., Jr. (2015) Herpes simplex type 2 virus deleted in glycoprotein D protects against vaginal, skin and neural disease. *eLife*. PMCID PMC4352706

DR. GANJAM V. KALPANA

Molecular Genetic Analysis of Tumor Suppressor INI1/hSNF5 in HIV-1 Replication and Cancer

INI1/hSNF5 is a component of the chromatin remodeling SWI/SNF complex. It is an interacting partner for HIV-1 integrase (IN) and also a tumor suppressor biallelically mutated in rhabdoid tumors, a rare but highly aggressive pediatric malignancy. The two major areas of focus in the laboratory are: (i) understanding the role of INI1 in HIV-1 replication and exploring its potential as a drug target for intervention of AIDS; and (ii) understanding the mechanism of tumor suppression by INI1/hSNF5 and developing novel and effective therapeutic strategies for rhabdoidtumors.

INI1 in HIV-1 replication: We have found that INI1/hSNF5 directly binds and recruits components of Sin3a-histone deacetylase (HDAC) complex into the HIV-1 virions and this HDAC1 complex appears to be required for viral infectivity. We are currently isolating and characterizing IN and INI1 mutants defective for binding to HDAC1 complex and testing their effect on HIV-1 replication. We have found that HIV-1 harboring IN mutants defective or binding to INI1 are severely compromised for replication. Furthermore, we have found that INi1 mutants defective for binding to HDAC1 complex dominant negatively inhibit HIV-1 but not SIV replication. These studies are likely to open up a new paradigm for role of INI1 in HIV-1 replication and may provide novel strategies to inhibit viral replication.

Mechanism of Tumor suppression by INI1/hSNF5: By using a series of genetic systems developed in our laboratory and by isolating cancer-associated mutations of INI1, and a wealth of protein-protein interaction defective mutants of INI1, we are dissecting the exact mechanism of INI1-medaited G0/G1 cell cycle arrest, mitotic arrest, and senescence and tumor suppression. Furthermore, characterizing the INI1-associated HDAC1 complex has revealed an unanticipated role of INI1 in interferon signaling and tumor suppression.

Development of targeted therapies for rhabdoid tumors based on INI1 function: One of the goals of our laboratory is to develop molecularly targeted therapies based on the understanding of genesis of rhabdoid tumors. Majority of rhabdoid tumors have biallelic inactivation of *INI1* gene. Our previous studies demonstrated that Cyclin D1 is a direct downstream target of INI1 mediated repression and that rhabdoid tumors are exquisitely dependent on Cyclin D1 for genesis and survival. Our preclinical studies have provided proof of principle for our hypothesis that targeting Cyclin/cdk axis is an effective means of inhibiting rhabdoid tumors *in vitro* and *in vivo*. The current goal is to develop novel strategies to facilitate clinical translation of laboratory findings to establish an effective therapy for these tumors. For this purpose, we are using non-invasive imaging technology such as microPET to monitor the therapeutic efficacy in primary mouse tumor models, developing novel drugs to target these tumors and investigating the interaction between *Cyclin D1*, the cdk pathway and *Ini1* in mouse models.

Identification of downstream pathways regulated by *INI1* has been instrumental in novel biomarkers and therapeutic targets for these tumors. *Aurora A* is repressed by *INI1* and it is de- repressed in rhabdoid tumors due to loss of *INI1*. We have found

that Aurora A is a novel therapeutic target as siRNA-mediated depletion of this gene resulted in potent mitotic catastrophe and cell death in rhabdoid tumors.

PUBLICATIONS

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Smith ME, Cimica V, Chinni S, Jana S, Koba W, Yang Z, Fine E, Zagzag D, Montagna C**, Kalpana GV.** Therapeutically targeting Cyclin D1 in primary tumors arising from loss of *Ini1.* Proc Natl Acad Sci U S A. 2011 Jan 4;108(1):319-24. Epub 2010 Dec 20.

Jennifer Cano and **Ganjam V. Kalpana.** Inhibition of early stages of HIV-1 assembly by INI1/hSNF5 transdominant negative mutant S6. J Virol. 2011 Mar; 85(5):2254-65. Epub 2010 Dec 15.

SeungJae Lee, Velasco Cimica, David Zagzag and **Ganjam V. Kalpana.** Aurora A Is a Repressed Effector Target of the Chromatin Remodeling Protein INI1/hSNF5 Required for Rhabdoid Tumor Cell Survival. Cancer Res. 2011 May 1;71(9):3225-35. Epub 2011 Apr 26.

DR. GEORGIOS KARAGIANNIS

THE RESPONSE OF TUMOR AND IMMUNE MICROENVIRONMENTS TO CYTOTOXIC CHEMOTHERAPY

Chemotherapy offers long-term clinical benefits to many patients with advanced cancer. However, recent evidence has linked the cytotoxic effects of chemotherapy with the *de novo* elicitation of a prometastatic and immunosuppressive microenvironment. This "modified" microenvironment is triggered by a wound healing-driven cytokine storm or via direct effects of certain chemotherapies on stromal and/or immune cells, the most critical of which are the tumor-associated macrophages. Such chemotherapy “educated” cells promote distant metastasis and immune evasion in the tumor microenvironment. Clinical studies offer substantial evidence that such immunosuppressive and prometastatic changes have been identified in certain patient populations, especially in those presenting with either minimal or partial pathologic response after neoadjuvant chemotherapy. To answer this complex research question repertoire, our newly founded creative team in Einstein operates in a multidisciplinary environment, in which we develop transgenic and xenograft mouse models of solid carcinomas (e.g., breast, pancretic, colorectal, etc), and utilize advanced microscopy (i.e., multiplex and high-throughput immunofluorescence techniques, multiphoton intravital imaging, electron microscopy), coupled to traditional and digital pathology pipelines, in an effort to outline the contextual prerequisites of chemotherapy-mediated immunosuppression in the primary tumor microenvironment, as well as in primary and/or secondary lymphoid organs.

Our lab particularly focuses on the following biological questions:
(1) *What is the role of key prometastatic cytokines/chemokines (e.g., Cxcl12) in driving contextual immunossuppression in the tumor microenvironment?* In this project, we develop cancer models of targeted Cxcl12/Cxcr4 disruption (e.g., conditional knock-out models, and/or mouse models of pharmacological Cxcl12/Cxcr4 inhibition, etc), to investigate immune cell topographies using multiplex immunofluoresce and image analyses.
(2) *What is the origin of immunosuppressive myeloid (macrophage and other myeloid suppressor) populations in the primary tumor microenvironment?* Here, we study “emergency” myelopoiesis, which is triggered primarily in extramedullary sites as a consequence of chemotherapy-mediated cytotoxic tissue damage and the ensuing cytokine surge (e.g., TNF-alpha). Our goal is to develop “anti-myelopoiesis” therapies against those niches to alleviate the sources of immunosuppression in the primary tumor microenvironment.
(3) *What is the role of the thymic environments in establishing anticancer immunity after treatment with cytotoxic chemotherapy?* Interestingly, acute thymic involution has been described as a principal mechanism for the decline of cancer immunosurveillance and anticancer immunity after treatment with cytotoxic chemotherapy. In this project, we develop mouse models of acute thymic involution to study the intrathymic pathways of regeneration following chemotherapy.
Taken together, our research program aims to decipher the immunosuppressive barriers during cancer progression, thus laying foundation for improving the current therapeutic modalities.

PUBLICATIONS:

Asiry S, Kim G, Filippou PS, Rivera Sanchez L, Entenberg D, Marks DK, Oktay MH, **Karagiannis GS.** The Cancer Cell Dissemination Machinery as an Immunosuppressive Niche: A New Obstacle Towards the Era of Cancer Immunotherapy. Frontiers in Immunology, 2021; 12: 654877.

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DR. LIBUSHA KELLY
http://www.kellylab.org/

My lab is interested in microbial communities as information-rich probes that report on many aspects of the ecosystem properties over space and time. We try to understand the fundamental rules governing how microbiomes sense, process, and respond to internal and external signals from their environments, and how they evolve—both as a community and as individuals—under changing environments.

Our work to date has identified new classes of gut chemistry as a previously unrecognized driver of microbial metabolism (including drug metabolism), discovered novel phage populations in the oceans, and pioneered computational approaches to improve analyses of—and inferences we can make from—data describing microbial ecology in complex systems.

Our future work has three primary drives: 1) opening new paths to non-invasive, inexpensive technologies for monitoring human and environmental health trajectories a developing microbiome-based therapies and interventions; 2) identifying ecosystem-level, taxonomy-independent, functional markers of gut microbiome health by characterizing interactions between diet, disease, the microbiome, and gut redox chemistry that is inseparably coupled with human metabolism; 3) understanding the role of mobile genetic elements as information integrators and carriers by developing AI/ML models to identify and characterize unrecognized mobile elements and map their activation and travel through microbes and microbiomes under environmental perturbations.

Complete Publication List:
https://scholar.google.com/citations?hl=en&user=sg7-rm4AAAAJ&view_op=list_works&sortby=pubdate

Selected Publications and Products:
(†= co-first author; *=co-corresponding author).

1. Flamholz ZN, Biller SJ, **Kelly L**. Large language models improve annotation of prokaryotic viral proteins. Nat Microbiol. 2024 Feb;9(2):537-549. doi: 10.1038/s41564-023-01584-8. Epub 2024 Jan 29. PMID: 38287147

2. Wolfson SJ, Hitchings R, Peregrina K, Cohen Z, Khan S, Yilmaz T, Malena M, Goluch ED, Augenlicht L, **Kelly L**. Bacterial hydrogen sulfide drives cryptic redox chemistry in gut microbial communities. Nat Metab. 2022 Oct;4(10):1260-1270. doi: 10.1038/s42255-022-00656-z. Epub 2022 Oct 20. PMID: 36266544.

3. Kauffman KM†, Chang WK†, Brown JM, Hussain FA, Yang J, Polz MF*, **Kelly L*.** Resolving the structure of phage-bacteria interactions in the context of natural diversity. Nat Comm. 2022 Jan 18;13(1):372. PMID: 35042853; PMCID: PMC8766483.

4. Guthrie L, Wolfson S, **Kelly L**. The human gut chemical landscape predicts microbe-mediated biotransformation of foods and drugs. Elife. 2019 Jun 11;8. doi: 10.7554/eLife.42866. PubMed PMID: 31184303; PMCID:PMC6559788.

5. Kauffman KM, Hussain FA, Yang J, Arevalo P, Brown JM, Chang WK, VanInsberghe D, Elsherbini J, Sharma RS, Cutler MB, **Kelly L*,** Polz MF*. A major lineage of non-tailed dsDNA viruses as unrecognized killers of marine bacteria. Nature 2018 Feb 1;554(7690):118-122. doi: 10.1038/nature25474. Epub 2018 Jan 24. PubMed PMID:29364876.

DR. MICHELLE LARSEN

Drug resistant TB

Tuberculosis (TB) is a significant global health burden. Although new TB drugs are advancing from bench to clinic, the rise of drug resistant TB (DR-TB) impedes progress of TB control programs. The World Health Organization estimated that in 2022 there were more than 545,000 new cases of drug resistant TB of which only one third of cases were diagnosed. Our lab focuses on two important aspects of DR-TB: (1) emergence of resistance and (2) rapid diagnosis.

Emergence of DR-TB

Given the slow doubling time of *Mycobacterium tuberculosis* (*Mtb*), the causative agent of TB, antibiotic treatment of DR-TB is 6 – 18 months and can include antibiotics that are injectable and/or have significant side effects. Bedaquiline (BDQ), the first new antibiotic approved for TB in over 40 years, is a well-tolerated antibiotic that targets ATP synthesis in *Mtb* and has become the cornerstone of an all-oral six month treatment course for DR-TB. TB and HIV are highly prevalent in the KwaZulu-Natal province of South Africa and was one of the first areas where BDQ was evaluated. Dr. Larsen has ongoing research projects with the Africa Health Research Institute (AHRI; formerly K-RITH) and CAPRISA in KwaZulu-Natal to better understand the baseline and emergence of *Mtb* resistance to BDQ. Embedded within a BDQ adherence clinical cohort, we have observed that 2.5% of the patients enrolled in the study had baseline resistance to BDQ, despite any previous BDQ exposure and another 2.5% of the patients had a BDQ susceptible *Mtb* isolate at baseline but BDQ resistance emerged months later even in patients with high adherence indicators. Although the target of BDQ is the ATP Synthase of *Mtb* all the mutations in DR-TB isolates in this cohort so far have been in the *mmpR5* (*Rv0678*) gene. MmpR5 (major mycobacterial protein) is a transcriptional repressor of the MmpS5/MmpL5 efflux pump so mutations in *mmpR5* lead to increased efflux pump abundance. However, not every mutation in *mmpR5* results in BDQ resistance so our lab is focusing on characterizing the most clinically relevant *mmpR5* variants.

Rapid Diagnosis of DR-TB The slow doubling time of *Mtb* means that culture-dependent approaches to determine drug susceptibility can take 4 – 6 weeks. Rapid molecular diagnostic approaches for TB have matured, however, for BDQ and many other drugs, molecular diagnostics are not effective as genotype does not necessarily predict phenotype. We have developed with collaborators a mycobacteriophage that can serve as a rapid reporter of phenotypic drug resistance. For this rapid assay, *Mtb* from sputum samples or culture is incubated with or without drug. Mycobacteriophage encoding a green fluorescent protein or luciferase are then used to infect *Mtb.* If an *Mtb* isolate is susceptible to a drug, there will be reduced reporter phage signal in the presence of the drug compared to the no-drug control. For an *Mtb* isolate resistant to a drug, the reporter phage signal will be similar in the drug and no-drug conditions. In collaboration with a clinical reference laboratory and co-Investigators at AHRI and CAPRISA we are testing clinical *Mtb* isolates with this newest generation of reporter phage.

Phage discovery workshop in South Africa to identify and engage students for future research in TB or HIV Beyond the utility of mycobacteriophages as diagnostic tools, they have also been the platform for education and resource development activities in an underserved population. Dr. Larsen has been co-founder and co-director of the Mycobacterial Genetics Course in Durban, South Africa. This discovery-driven two-week workshop has been held 11 times in the last 15 years with over 280 students participating. The workshop has both bench and bioinformatic components. For benchwork, each student discovers a novel mycobacteriophage then characterizes their phage including purification, electron microscopy, and sub-type classification. For bioinformatics small

groups of students work to annotate the genome of a phage that was discovered in the previous workshop with that annotation being published to GenBank at the end of the two-week workshop. Of note, a phage isolated in the second year of the workshop was recently used in a phage cocktail to treat a patient with a non-tuberculous mycobacterial infection.

Emergence of novel zoonotic TB

Keeping with the theme of emergence, our lab also studies *Mycobacterium mungi*, a novel mycobacterial strain that causes TB in nine-banded mongoose in northern Botswana. Dr. Larsen has been co-founder and co-organizer of a nine meeting series over the last 15 years to bring together researchers and clinicians that work on mycobacterial diseases. The 'Many Hosts of Mycobacteria' meeting is a small discussion focused meeting that includes research and clinicians that work on human TB (*M. tuberculosis*, *M. africanum*), wildlife and livestock TB (*M. bovis; M. mungi*), leprosy (*M. leprae*), Buruli ulcer (*M. ulcerans*) and non-tuberculous mycobacterial diseases. The genesis of this meeting was Dr. Larsen's extensive work on multi-species of pre-clinical animal models for TB/HIV vaccine development. The collaboration for the *M. mungi* project was a result of a Many Hosts of Mycobacteria meeting. For this project our lab collaborated to complete the whole genome sequence of *M. mungi* and to develop a transcriptomics biomarker panel to predict *M. mungi* disease state of mongoose in a fieldwork setting. Ongoing and future studies include molecular epidemiologic studies of *M. mungi* infection across multiple mongoose troops to better understand environmental, host, and bacteriological contributors to *M. mungi* pathogenesis.

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DR. GREGOIRE LAUVAU

Immune effector cell differentiation & protective host responses against microbial pathogens and tumors *in vivo*

My laboratory investigates i) the biology of T lymphocytes, how they differentiate, form memory and mediate vaccinated host protection or immune homeostasis, ii) immune mechanisms of defense against malaria, iii) the tumor immune microenvironment and new immunotherapeutics against cancer. We use various models of immunization or infection that include the intracellular bacterium Listeria monocytogenes, and viruses such as the Vesicular Stomatitis virus and the lymphochorionmeningitis virus. We study the immune response to the parasite Plasmodium that causes malaria in surrogate mouse models and in human patients. We also investigate how known human breast cancer driver mutations with poor prognosis impact immune functions. We take advantage of a range of advanced fluorescent-tracer based methodologies and intravital microscopy to monitor and visualize immune cells in situ. We use cell transfer experiments and novel genetically modified mice models in which dynamic cell functions can be monitored and/or in which functional subsets of immune cells can be selectively eliminated. We also make use of the latest cutting-edge approaches to phenotype immune cells that include high dimensional flow cytometry, single cell expression and epigenetic profiling, and designs of new immunotherapeutic biologics. Overall, the goal of my laboratory is to improve our mechanistic understanding of the factors that orchestrate antimicrobial and antitumoral host protective immune responses in vivo. Using the knowledge generated by our work, we are building new generation immunomodulatory strategies for the next generation treatments

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21. **Lauvau G.**, Loke P., Holh T.M. Monocyte Mediated Defense Against Pathogenic Microbes. 2015. **Seminars in Immunology 2016**, 27:397-409.

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DR. JACK LENZ

Area of Research: ***Retroviruses. Evolution of human endogenous retroviruses, and their roles in normal functions and diseases. Retrovirus gene expression. Pathological consequences of virus DNA integration into host genomes.***

DR. THOMAS S. LEYH

My laboratory is focused on understanding the molecular basis of life. Our interdisciplinary pursuit of this issue has provided a broad experimental platform for our work and has proven a recipe for discovery. For example, my group discovered the link between sulfur biology and GTPase function; a linkage that rests with the enzyme ATP sulfurylase, which allosterically couples the chemical potential of GTP hydrolysis to the synthesis of activated sulfate (*APS,* adenosine 5'-phosphosulfate), an essential sulfur metabolite. Our inquiries in this area have revealed further that this same enzyme forms a complex with its partners in the cysteine biosynthetic pathway, and, remarkably, that new catalytic function emerges from this complex - the hydrolysis of ATP. In this case, it is the energy of ATP hydrolysis that is linked to the synthesis of APS. This finding underscores how cellular components can combine in synergistic ways to create hierarchies of function. Such hierarchies, whose behaviors are rooted in the reduction of entropy, are not well understood, and are of keen interest to us. First principles of chemistry and enzymology suggested that ATP sulfurylases that are not linked to an external energy source, such as ATP or GTP hydrolysis, might transfer APS directly to the active site of the next enzyme in the metabolic pathway, APS kinase. We have shown that in a spectacular display of the interplay of structure and function, certain sulfate activating complexes transfer APS directly between the active-sites of ATP sulfurylase and APS kinase *via* a 75Å-long groove that opens and closes in response to the position of the nucleotide within the groove.

Transfer of the sulfuryl-moiety (- SO_3^-) from activated sulfate to biological acceptors is used widely by the cell to regulate metabolism, and the extent to which a particular metabolite is sulfated is determined by the balance of the *in-vivo* activity of the sulfotransferase (which transfers the sulfuryl-group) and sulfatase (which hydrolytically removes it). Compelling, disease-relevant biology pivots on the activities of each of the six known cytosolic sulfotransferase isozymes. Our laboratory has concentrated primarily on estrogen sulfotransferase (EST), which sulfates estrogen and thereby prevents it from binding to and activating the estrogen receptor. Aberrant sulfation of estrogen is tightly, causally linked to cancer in primary estrogen-dependent breast tumors. We have recently determined the first transition-state structure of an enzyme catalyzed sulfuryl-transfer reaction – that of EST. While it is quite gratifying to "see" precisely how the electronic structure of the bonds involved in the transfer reorganizes as enzyme-bound substrate moves between their ground- and transition-states, the structure is also of considerable practical value in that it defines the target for the design and synthesis of sulfuryl-transfer transition-state inhibitors (a perfect transition-state mimic is expected to inhibit with picomolaraffinity).

Streptococcus pneumonia, a multiple-drug resistant organism, is estimated to take the lives of 3600 people daily, the majority of whom are children and the elderly. We discovered recently that mevalonate kinase, an essential enzyme in the isoprenoid biosynthetic pathway in *Streptococcus pneumoniae*, is potently allosterically inhibited by diphposphomevalonate (*DPM*), a downstream intermediate in the pathway, and that the human isozyme is not. Genetic and animal studies of this multiple-drug resistant organism have taught us that the mevalonate pathway is essential for the survival of *S. pneumonia* in the lung, and human serum. Consequently, we have undertaken a major research effort to develop novel antibiotics that target these enzymes in gram-positive bacteria. The program, carried out under the auspices of the *NIAID*, brings together an interdisciplinary team of faculty, postdoctoral fellows and graduate students in the areas of high-resolution NMR-spectroscopy, crystallography, synthetic chemistry, and biochemistry to explore fundamental issues of allostery, catalysis, and inhibition in these systems. I am pleased to report that our recent efforts have produced inhibitors that act with nanomolar affinity at each of multiple points in the pathway, and are capable of killing infectious *S. pneumonia* in rich media at ~ 25 □g/ml.

The three projects outlined above comprise the core of our research activities; however, we are also expanding into two new areas. The etiology of how *M. tuberculosis* emerges from dormancy in the lung tubercle is not yet well understood. We are beginning to define the molecular logic of this transition with Prof. John Chan, an expert mycobacteriologist who has isolated a mutation that activates growth by derepressing dormancy. While the protein that harbors this mutation has not yet been assigned molecular function, we now know that it co-purifies with one-equivalent of adenine nucleotide bound to it, that it slowly hydrolyses ATP, and that its sequence identifies it as a possible element of a signaling network – we are currently testing this hypothesis using genetic and biochemical assays. In a final program, we are collaborating with a single molecule spectroscopist, and biological chemist at Columbia University to better understand and control the ribosomal editing functions of the protein-synthetic machinery toward mis-acylated tRNA. Editing protects against disease by recognizing and rejecting misacylated tRNA; controlling editing gives way to regiospecific incorporation of non-natural amino acids into proteins, which will facilitate myriad scientific endeavors including single-molecule exploration of the cellular *milieu*.

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DR . KERRY MURPHY

My clinical translational research is focused on the impact of reproductive hormones, both endogenous and exogenous on genital tract mucosal immunity and the vaginal microbiome in HIV-infected and at-risk women. The goal of this work is to identify the biologic mechanisms that mediate changes in genital tract immunity and the vaginal microbiome in the setting of high progesterone states e.g. progesterone-dominant hormonal contraceptives and low estrogen states e.g. menopause as these states represent periods of vulnerability for HIV acquisition and transmission. The long-term goal of this research is to develop targeted interventions to augment these hormonally responsive changes in the genital tract in order improve genital tract health and HIV prevention.

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DR. JOSHUA D. NOSANCHUK

Key Words: fungus, histoplasmosis, cryptococcosis, candidiasis, melanin, nitric oxide, tissue regeneration

Dr. Nosanchuk is the Senior Associate Dean for Medical Education and a physician-scientist who maintains a basic science laboratory that focuses on virulence factors in pathogenic fungi. Current areas of interest are 1) the role fungal extracellular vesicles in pathogenesis, 2) disease modification by monoclonal antibodies and 3) fungal melanin. Dr. Nosanchuk is also active in wound healing research and he collaborates with Drs. David Sharp and Joel Friedman (Dept. of Physiology and Biophysics) on translational projects pertaining to Fidgetin-like 2 and nitric oxide nanoparticles, respectively.

Dr. Nosanchuk is a senior physician-scientist-educator studying virulence factors in pathogenic fungi and novel therapeutics for fungi and tissue regeneration. Current areas of interest in fungal pathogenesis are the role of fungal extracellular vesicles in pathogenesis, disease modification by monoclonal antibodies, and how fungal melanin contributes to virulence. Dr. Nosanchuk also has active projects focusing on the development of nitric oxide micro- and nano-particles as novel therapeutics as well as the role of fidgetin-like 2 on tissue regeneration.

PUBLICATIONS

Dr. Nosanchuk has over 350 peer-reviewed publications:

https://pubmed.ncbi.nlm.nih.gov/?term=nosanchuk&sort=date

DR. LIISE-ANNE PIROFSKI

The focus of the Pirofski laboratory is on antibody and B cell immunity to encapsulated microbes using *Streptococcus pneumoniae* (Pneumococcus) and *Cryptococcus neoformans* (Cryptococcus) as examples. Both of these microbes cause disease in normal and immunocompromised people, particularly those with HIV infection, AIDS, B cell and antibody defects. The laboratory conducts translational studies of the serological, cellular, and molecular response to these microbes in normal and immunocompromised patients and basic scientific studies of microbial pathogenesis and host-microbe interaction. The goals of this research areto understand how innate and acquired antibody and B cell immunity to these microbes confers resistance to disease and to translate this knowledge into novel approaches to treatment and prevention of pneumococcal and cryptococcal disease.

PUBLICATIONS

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DR. STEVEN PORCELLI

Improving T cell responses for vaccination and disease prevention

Our laboratory studies the control of acquired immune responses by T cells, which we view as the master regulators and key effectors of host defense and immune tolerance. In broad terms, our research can be divided into two interrelated areas. The first is to understand the role of regulatory T cells, with particular emphasis on the activities of a specialized T cell subset known as CD1d-restricted NKT cells. These T cells have the highly unusual property of responding to specific glycolipid antigens, and we are studying ways to control their regulatory and effector functions in various mouse models of disease. A second second major research area is the study of T cell responses against pathogenic microorganisms, especially *Mycobacterium tuberculosis.* We have recently made significant progress in understanding how mycobacteria block effective host T cell responses, and we are now working to incorporate our findings into the rational and intelligent design of a new tuberculosis vaccine. In the short term, we hope to broaden our understanding of how organisms like *M. tuberculosis* successfully evade eradication by the immune system. Our major long term goal is to create a genetically or chemically modified live attenuated *M. tuberculosis* strain that will be safe and effective as a vaccine against tuberculosis. The laboratory has also recently developed interests in novel cancer vaccines, tumor-specific immunotherapies and immunity against emerging viral threats such as Ebola and Zika viruses, and is pursuing several projects in these areas.

PUBLICATIONS

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Nat Microbiol (9):16133 (2016). PMID: 27562263

DR. VINAYAKA PRASAD

Research in our laboratory is focused on two areas of HIV/AIDS: how beta chemokines modulate ESCRT proteins to augment HIV-1 replication and the viral determinants of HIV associated neurocognitive disorders (HAND).

HIV-1 budding, a novel target for therapeutics: We have reported, for the first time, an external stimulus that enhances ESCRT complex-mediated budding and release of HIV-1 from the infected cells. We show that the mechanism by which the β chemokine, CCL2, enhances virus production is by mobilizing ALIX, a key adapter protein of the ESCRT complex III from the cellular actin cytoskeleton to the sites of virus budding and release. ESCRT complexes are essential for the membrane scission step in the bud neck of viruses. We show that CCL2, which is induced upon HIV-1 infection of macrophages, stimulates the budding and release of HIV-1 clade B (HIV-1B), but not that of HIV-1 clade C (HIV-1C), which does not induce CCL2. We also show that immunodepletion of CCL2 strongly inhibits (10-fold) virus production from macrophages. We have shown that the ability to respond to CCL2 levels is dependent on the presence of late motif 2 or LYPX in HIV-1 Gag, which recruits ALIX to facilitate virion budding. We show that clade C viruses have a highly conserved absence of the LY dipeptide. We also show that the absence of LY contributes to reduced replication fitness of HIV-1C. Interestingly, variants of clade C HIV-1 in India and Africa that have acquired increased replication fitness display novel tetrapeptide insertions in Gag-p6 precisely where the LY dipeptide is missing. These viruses have regained the ability to bind ALIX, are more fit and respond to CCL2.

The lab is currently beginning a study of naturally occurring polymorphisms in *ccr2* or *ccl2* genes that are known to affect HIV-1 disease. A V64I mutation in *ccr2* gene is known to delay HIV disease progression by up to 4 years and an enhancer mutation in *ccl2* is known to enhance plasma CCL2 levels and is preferentially enriched in HIV-infected individuals. We are studying the effect of each of these mutations on the CCL2-mediated ALIX mobilization and HIV-1 budding/release and viral fitness.

HIV associated Neurocognitive Disorders (HAND): The severe form of HAND, the HIV associated dementia (HAD), is common among clade-B HIV-infected individuals in the US, but less common among individuals infected with clade-C HIV-1 in India, suggesting clade-specific differences in neuropathogenicity. Understanding clade-specific determinants of neuropathogenesis may shed light on the disease mechanism and help develop targeted drugs for HAD. We previously demonstrated that due to a C31S polymorphism, clade C Tat lacks the chemokine function of Clade B Tat that plays a crucial role in an increased brain infiltration of monocytic phagocytes in HAD. We studied neuropathogenesis induced by two HIV-1 clades B and C using SCID mouse HIV encephalitis (SCID-HIVE) model and reported that while the introduction of clade B HIV-1ADA into SCID mouse brain recapitulates the key features of human HAD disease, mice exposed to similar inputs of HIVIndie-C1 (clade C) made fewer memory errors than those exposed to HIV-1ADA (clade B). HIV-1ADA also caused greater astrogliosis and loss of neuronal network integrity.

Work from many groups has shown that clade C HIV-1 in Southern Africa can induce HAD at much higher incidence than in India. We hypothesized that such variation is due to polymorphism in the neuropathogenesis determinants in Tat or gp120, the two major neurotoxicity determinants of HAND. With respect to Tat, we observed that the percentage of HIV isolates with dicysteine motif in Tat is 2-3% on the Indian subcontinent while in the Southern African countries, they ranged from 19-26%. These data broadly correlate with the HAD frequencies reported from India, South Africa and Botswana (3-4%, 25% and 38% respectively). This finding has been corroborated using a Zambian HIV-1C isolate that displays a C31 residue and thus an intact dicysteine motif. Our in vitro and SCID-HIVE results clearly indicate that Tat dicysteine motif determines neurovirulence. If confirmed in population studies,

it may be possible to predict neurocognitive outcomes of individuals infected with HIV-1C by genotyping Tat.

Since Tat is not the only neurovirulence determinant in HIV-1, we examined whether gp120 exhibits intra-clade differences between India and Southern Africa. Our findings indicate that gp120 can also display region-specific differences. For example, the Southern African HIV isolates appear to contain more robust neurovirulence determinants than those in the Indian isolates. Thus, two different viral genes in India appear to show determinants of low neurotoxicity. These results suggest that clinical studies studying the incidence of HAD or HAND to correlate viral genetic differences must examine both Tat and gp120. *Ongoing work in our laboratory is attempting to identify the neurovirulence signatures of gp120 in clade C and clade B virus isolates and exploring the role of exosomes in neurovirulence*.

PUBLICATIONS

HIV-1 budding, a novel target for therapeutics

David Ajasin, Vasudev R. Rao, Xuhong Wu, Santhamani Ramasamy, Mario Pujato, Arthur P. Ruiz, Andras Fiser, Anne Bresnick, Ganjam V. Kalpana and Vinayaka R. Prasad (2019) CCL2 Mobilizes ALIX to Facilitate Gag-p6 Mediated HIV-1 Virion Release. eLIFE 2019;8:e35546 doi: 10.7554/eLIFE.35546.

HIV Neuropathogenesis

Arthur P. Ruiz, David Ajasin, Santhamani Ramasamy, Eliseo Eugenin and Vinayaka R. Prasad (2019) A Naturally Occurring Polymorphism in the HIV-1 Tat Basic Domain Inhibits Uptake by Bystander Cells and Leads to Reduced Neuroinflammation. Scientific Reports 9:3308

Rao, V., Neogi, U., Talboom, J. S., Padilla, L., Rahman, M., Fritz-French, C, Gonzalez-Ramirez, Verma, A., Wood, C., Ruprecht, R. M., Ranga, U., Azim, T., Joska, John, Eugenin, T., Shet, A., Bimonte-Nelson, Tyor, W. R. and Prasad, V. R. (2013) Clade C HIV-1 isolates circulating in Southern Africa exhibit a greater frequency of dicysteine motif-containing Tat variants than those in Southeast Asia and cause increased neurovirulence. Retrovirology 10:61. DOI: 10.1186/1742-4690-10-61.

Rao, V. R., Sas, A., Eugenin, E., Siddappa, N. B., Bimonte-Nelson, H., Berman, J., Ranga, U., Tyor, W. R. and Prasad, V. R. (2008) HIV-1 clade-specific differences in the induction of neuropathogenesis. J. Neurosci. 28:10010-6.

DR. CHAIM PUTTERMAN

Area of Research: ***Mechanisms of autoimmunity; Pathogenesis of kidney and neuropsychiatric disease in systemic lupus erythematous (SLE), including anti-DNA antibodies, macrophages, and cytokines; Novel therapies for lupus; SLE biomarkers***

Systemic lupus erythematosus (SLE) is a prototypical systemic autoimmune disease, characterized by the presence of numerous autoantibodies and involvement of multiple organ systems. Inflammation of the kidneys, or lupus nephritis, appears in up to 50% of lupus patients during the course of their disease. Despite medical treatment, morbidity and mortality from renal disease are all too common in lupus patients, with reports of 5-year renal survival ranging from 46-95%. Overall increases in the incidence of lupus and in the number of deaths from the disease reported in the United States are additional reasons for significant concern for clinicians and researchers alike. Unfortunately, major strides forward in understanding lupus and the advent of newer "biologic" therapies in the field of Rheumatology have yet to translate into measurable benefits for the majority of patients with SLE. Current treatments, while effective, only control disease activity but are not curative. Furthermore, therapeutic modalities that are employed at this time for the treatment of patients with lupus are non-specific - and commonly affect normal cells that are essential for the defense against foreign pathogens, in addition to suppressing the disease-relevant autoreactive B cells. Nevertheless, early diagnosis and prompt treatment can still significantly improve long-term prognosis.

Anti-double stranded (ds) DNA antibodies are a serologic hallmark of patients with SLE. In recent years it has been increasingly clear that not only are anti-dsDNA antibodies an important diagnostic marker for lupus, but that these autoantibodies are also instrumental in the pathogenesis of lupus nephritis. The mechanisms by which anti-dsDNA antibodies induce renal injury, however, are not completely understood. It has been suggested that anti-dsDNA antibodies bind DNA in the circulation followed by non-specific deposition of these immune complexes in the kidney, or that in-situ immune complexes are formed in the kidney by binding of anti-dsDNA antibodies to nuclear antigens deposited on the glomerular basement membrane. Alternatively, some anti-dsDNA antibodies may cause injury by penetrating into living cells and affecting metabolic pathways. Finally, we and others have generated evidence that strongly suggests that at least some anti-dsDNA antibodies are pathogenic not by virtue of their affinity for DNA, but rather by direct cross-reactivity with renal antigen.

One major long-term goal of the laboratory is to study the renal pathogenicity of anti-dsDNA antibodies. We are determining the cross-reactive kidney antigen bound by anti-DNA antibodies in human lupus and in mouse models of the disease to understand what determines the nephritogenic potential of these antibodies. We made significant progress in defining one renal antigen bound by cross-reactive anti-DNA antibodies. We discovered that a-actinin is a major cross-reactive target for the anti-dsDNA antibody response in murine lupus, and that both human monoclonal and polyclonal anti-dsDNA antibodies bind to a-actinin as well. In current studies, we are investigating if a-actinin can serve not only as a target but also as an antigenic trigger for anti-DNA antibodies, whether anti-a-actinin antibodies are associated with specific disease features (analysis of patient cohorts), and what might be the mechanism by which these antibodies induce damage in kidney cells (proteomic and microarray approaches). Understanding the renal pathogenicity of cross-reactive anti-dsDNA antibodies by identifying the target antigen for these antibodies in the kidney would improve our understanding of a key manifestation of lupus and would facilitate the development of serological tools to better predict the onset and severity of renal involvement in patients with SLE. Furthermore, identification of the triggering and/or target antigen in lupus will allow us to develop novel approaches to the treatment of lupus, by blocking the effects of anti-DNA antibodies on target organs or by specifically tolerizing pathogenic B cells.

Members of the TNF-superfamily of ligands are centrally involved in normal immune responses, and in the pathogenesis of autoimmune disorders. In a second group of related projects in the laboratory, we are investigating the role of a relatively new member of the TNF superfamily (TWEAK) and its receptor Fn14 in the pathogenesis of lupus, specifically lupus nephritis. We have shown that TWEAK induces a pro-inflammatory profile of cytokines and chemokines in kidney epithelial and mesangial cells, and thus contributes to the influx of inflammatory cells observed in the early stages of lupus nephritis. Modulation of the TWEAK/Fn14 pathway in SLE may be an important target for novel therapies for this disease. Furthermore, we are exploring the role of TWEAK as a biomarker for disease activity in lupus nephritis. Indeed, such as serum or urinary biomarker would have tremendous value for patient care, allowing early and accurate diagnosis and more precise

management, without the need for an invasive kidney biopsy.

DR. DAVID ROSENSTREICH

Area of Research: ***Chronic urticaria treatment; asthma epidemiology; chronic sinusitis epidemiology; immunological effects of mercury***

Dr. David Rosenstreich is Professor of Medicine, Otolaryngology, and Microbiology and Immunology; Chief of the Division of Allergy and Immunology; and Director of the Bronx Asthma Project. His research currently focuses on the effects of inorganic dietary factors on immune reactivity in humans (specifically, the effects of mercury and acrylamide on human lymphocyte and monocyte production of TH1 and TH2 cytokines in vitro).

Dr. Rosenstreich completed medical school at NYU School of Medicine and an internal medicine residency at the Bronx Municipal Hospital Center. He spent ten years as an investigator for the National Institutes of Health (NIH), National Institute of Allergy and Infectious Diseases (NIAID) and National Institute of Dental Research (NIDR) and was a visiting professor at the Rockefeller University Laboratory of Cellular Physiology and Immunology. He currently serves on the NIAID/NIH Data Safety Monitoring Board.

Dr. Rosenstreich has published over 170 articles, invited papers, and reviews, and has edited three books.

PUBLICATIONS: (Partial listing from over 170 research articles, invited papers and reviews and 3 edited books)

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2. Armenaka, M. and **Rosenstreich, D.L**.: The pathophysiology of chronic urticaria. Clin. Rev. Allergy, 1992; 10:257-279.
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13. Senturia YD. Bauman LJ. Coyle YM. Morgan W. **Rosenstreich DL**. Roudier MD. Mitchell H. Gruchalla R. Crain EF. The use of parent report to assess the quality of care in primary care visits among children with asthma. Ambulatory Pediatrics. 1:194-200, 2001

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21. Jariwala SP, Moday H, de Asis ML, Fodeman J, Hudes G, de Vos G**, Rosenstreich D.** The Urticaria Severity Score: a sensitive questionnaire/index for monitoring response to therapy in patients with chronic urticaria. Ann Allergy Asthma Immunol. 102:475-82, 2009
22. Fodeman J, Jariwala S, Hudes G, Wittner M, Klapper P, Liu Q, **Rosenstreich D.** Scratching the surface. Am J Med. 123:22-6, 2010

DR. YVONNE SAENGER

Area of Research: ***Biomarkers for early-stage melanoma Immunotherapy for hepatocellular cancer Immunotherapy biomarkers for solid tumors***

Dr. Yvonne Saenger is an expert in cancer immunotherapy with a focus on melanoma and gastro-intestinal tumors

The Saenger laboratory research immune biomarkers for melanoma recurrence to stratify patients for adjuvant immunotherapy. Digital pathology and artificial intelligence methods are used.

A second area of focus is analysis of the tumor immune micro-environment in liver cancer, particularly on studying human specimens and organoids to define the role of immune cell populations and complement in tumor progression.

PUBLICATIONS

Gartrell-Corrado RD, Chen A, Rizk EM , Marks DK, Bogardus M, Hart TD, Silverman AM, Bayan CA, Finkel G, Barker L , Komatsubara KM, Carvajal RD, Horst BA, Chang R, Monod A , Rabadán R, **Saenger Y**, "Linking transcriptomic and imaging data defines features of a favorable tumor immune microenvironment and identifies a combination biomarker for primary melanoma," *Cancer Research.* 2020 Mar 1;80(5):1078-1087. PMID: 31948941

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Gartrell RD, Marks DK, Rizk EM, Bogardus M, Gerard CL, Barker LW, Fu Y, Esancy CL, Li G, Ji J, Rui S, Ernstoff MS, Taback B, Pabla S, Chang R, Lee SJ, Krolewski JJ, Morrison C, Horst B, **Saenger YM, "**Validation of Melanoma Immune Profile (MIP), a Prognostic Immune Gene Prediction Score for Stage II-III Melanoma," *Clinical Cancer Research,* 2019 Jan 15 PMID: 30647081

Zhao J, Chen AX, Gartrell RD, Silverman A, Aparicio L, Chu T, Bordbar D, Shan D, Samanamud J, Goetz M, Yagamuchi JT, Cloney M, Horbinski C, Lukas RV, Raizer J, Rae AI, Yun J, Canoll P, Bruce JN, **Saenger YM**, Sims P, Iwamoto FB, Sonabend AM, Rabadan, R. "Longitudinal genomic study of response to anti-PD-1 immunotherapy in Glioblastoma Multiforme*," Nature Medicine 2019* Mar 25(3):462-469 PMID: 30742119

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Gartrell RD, Enzler T, Kim PS, Fullerton BT, Fazlollahi L, Chen AX, Minns HE, Perni S, Weisberg SP, Rizk EM, Wang S, Oh EJ, Guo XV, Chiuzan C, Manji GA, Bates SE, Chabot J, Schrope B, Kluger M, Emond J, Rabadán R, Farber D, Remotti HE, Horowitz DP, **Saenger YM.** Neoadjuvant chemoradiation alters the immune microenvironment in pancreatic ductal adenocarcinoma, Oncoimmunology. 2022 May 5. PMID: 35558160

DR. MARIA SOSA

Laboratory of Cancer Metastasis.

Perhaps the most difficult challenge in cancer research and treatment is the management of metastasis, the leading cause of death in cancer patient. However, the discovery that cancer patients treated for their primary tumor, can carry dormant disseminated cancer cells (DCCs) for years before reactivating to form incurable metastasis, opened a window of opportunity to prevent metastatic relapse.
Our interest is to explore the intrinsic and microenvironmental mechanisms that contribute to the establishment and maintenance of minimal residual disease that precedes metastasis in cancer patients. In particular, my lab focuses on understanding the biology of DCC dormancy, the origins of DCCs, the crosstalk between DCCs and immune cells and the role of transcriptional and pluripotency programs in regulating the fate of DCC dormancy and reactivation. We are particularly interested in determing how to therapeutically target innate immune evasion in dormant DCCs, with the idea to eradicate DCCs and thus, prevent metastasis formation. In this regard, we have two active grants focused on elucidating the mechanisms of interactions between dormant DCCs and innate immune cells (*Susan G. Komen* and *Pershing Square Shon Cancer Research Alliance*, see below).

Current Grant Funding.

Susan Komen Grant (Sosa, PI)
10/13/22-10/12/25
Targeting ZFP296 to Promote Inactivity of Early Metastatic Breast Cancer Cells.

The Pershing Square Shon Cancer Research Alliance **(**Sosa, PI)
07/01/22-06/31/25
Crosstalk and immune education by evolutionarily distinct disseminated cancer cells during the invisible phase of metastasis.

NIH/R01CA266443 **(**Sosa, PI)
09/01/22-08/31/27
Functional analysis of distinct and co-existing transcriptional programs regulating tumor dormancy.

Gilead's Research Scholar Programs **(**Sosa, PI)
09/01/23-08/31/25
Novel therapeutic strategies to prevent melanoma metastasis.

Publications (selected 5 papers from 2021)

1. Singh DK, Farias E, Carcamo S, Hasson D, Sun D, Cheung J, Nobre AR, Kale K, **Sosa MS**, Bernstein E, and Aguirre-Ghiso JA**#**. "Epigenetic reprogramming of DCCs into dormancy suppresses metastasis via restored TGFβ–SMAD4 signaling**" Cell Report**, 2023. doi: 10.3390/cancers11050726.

2. Jose Javier Bravo-Cordero**#**, Thomas U. Marron , **Sosa MS**, Juan Arriaga, Andrew L., Poulikos I. Poulikakos**#**. "Frontiers of Medical Research: Cancer Turning remission into cures: Novel therapies to outpace drug resistance and metastasis." **Frontiers of Medical Research: Cancer**, **Science**, 2023.

3. *Rodriguez-Tirado C, *Kale N, Carlini MJ, Shrivastava N, Alcina Rodrigues, Khalil B, Bravo-Cordero JJ, Yan Hong, Alexander M, Ji J, Fariba Behbod, and **Sosa MS**#. "NR2F1 is a barrier to dissemination of early stage breast cancer cells". **Cancer Research**, 2022. DOI:10.1158/0008-5472.CAN-21-4145. #corresponding author.

4. Borriello L., Coste A., Traub B., Sharma V., Karagiannis G., Lin Y., Wang Y., Ye X., DuranC., Chen X., Friedman M., **Sosa MS**, Sun D., Dalla E., Singh D., Oktay M., Aguirre-Ghiso J., Condeelis J. **#** and Entenberg D**#**. "Primary tumor associated macrophages activate programs of invasion and dormancy

in disseminating tumor cells". **Nature Communications**, 2022 Feb 2;13(1):626. doi: 10.1038/s41467-022-28076-3.

5. Khalil B, Sanchez R, Rhaman T, Moritsch S, Rodriguez Martinez A, Farias E, Cheung JF,Nobre AR, Kale N, **Sosa MS#** and Aguirre-Ghiso JA#. "A specific agonist of the orphan nuclear receptor NR2F1 suppresses metastasis through the induction of cancer cell dormancy". **J. Exp. Med.,** 2021. doi: 10.1084/jem.20210836. **#** co-corresponding authors.

DR. YARON TOMER

Dr. Tomer's research program focuses on the immunogenetic, epigenetic, and environmental mechanisms underlying thyroid autoimmunity, and type 1 diabetes, and on targeting these mechanisms in order to develop novel therapies. His group made several discoveries including identifying new genes and mechanisms underlying the strong association between type 1 diabetes and autoimmune thyroiditis; demonstrating that CD40 and thyroglobulin are major susceptibility genes for thyroid autoimmunity; identifying a unique amino acid variant in the peptide binding pocket of HLA-DR that is key for the development of thyroid autoimmunity; dissecting the epigenetic mechanisms by which polymorphisms in the thyroglobulin and TSHR genes interact with environmental agents (e.g. viruses) to trigger thyroid autoimmunity; and identifying a novel small molecule that can block antigen presentation in autoimmune thyroiditis.

Current Projects:

1. **Genetic and epigenetic studies in thyroid autoimmunity**
   The Tomer lab mapped several susceptibility genes for autoimmune thyroid diseases (AITD) including CD40, thyroglobulin, and TSHR. Recent data suggest that variants in regulatory regions of some of these genes interact epigenetically with environmental factors (e.g., viral infections) to trigger disease. Current studies are using epigenomic screening, including whole genome methylation studies and ChiP-seq analyses to study these genetic-epigenetic interactions.
2. **Epigenetic studies in type 1 diabetes**
   Similar studies are utilizing epigenomic screening to analyze epigenetic interactions between known type 1 diabetes susceptibility genes and interferon alpha, a key cytokine secreted during viral infections.
3. **Translational studies in autoimmune thyroiditis (AITD) and type 1 diabetes**
   The Tomer lab discovered that the presence of arginine at position beta-74 of the peptide binding pocket of HLA-DR is critical for the development of AITD. This discovery led to a translational project aimed at blocking thyroid antigen presentation to T-cells by the arginine beta-74 HLA-DR peptide binding pocket as a potential therapy for AITD. Recently, the Tomer lab identified a small molecule, Cepharanthine, that can block antigen presentation and suppress AITD in mouse models. Similar studies are performed in type 1 diabetes where the aim is to block the HLA-DQ8 peptide binding pocket from presenting insulin peptides to T-cells as a novel strategy to treat autoimmune diabetes.
4. **Genetic and functional analyses of autoimmune polyglandular syndrome (APS) type 3**
   The co-occurrence of type 1 diabetes and autoimmune thyroiditis in the same individual is considered a variant of the APS type 3 syndrome. The Tomer lab discovered several new susceptibility genes for APS3. The lab is now analyzing the mechanisms by which these genes predispose to disease.
5. **The role of viruses in triggering autoimmune thyroiditis and type 1 diabetes**
   Certain infections, such as hepatitis C, are associated with autoimmune thyroiditis and diabetes. Current studies are aimed at dissecting the mechanisms by which interferon alpha, the primary cytokine secreted during viral infections, can trigger autoimmune thyroiditis and diabetes in genetically susceptible individuals.

PUBLICATIONS

1. Menconi F, Monti MC, Greenberg DA, Oashi T, Osman R, Davies TF, Ban Y, Jacobson EM, Concepcion ES, Li CW, **Tomer Y.** Molecular amino acid signatures in the MHC class II peptide binding pocket predispose to autoimmune thyroiditis in humans and in mice. Proc Natl Acad Sci USA 2008; 105: 14034-14039.
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9. **Tomer Y**, Dolan LM, Kahaly G, Divers J, D'Agostino Jr. RB, Imperatore G, Dabelea D, Marcovina S, Black MH, Pihoker C, Hasham A, Hammerstad SS, Greenberg DA, Lotay V, Zhang W, Monti MC, Matheis N. Genome wide identification of new genes and pathways in patients with autoimmune thyroiditis and type 1 diabetes. J Autoimmun 2015; 60: 32-39.
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DR. XINGXING ZANG

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Our laboratory focuses on new immune checkpoints and new immunotherapies: From discoveries to clinical trials. We have discovered new members of the T cell costimulatory/coinhibitory B7 family and CD28 family, including B7x, HHLA2 and TMIGD2, and have identified new immune pathways of HHLA2-KIR3DL3, HHLA2-TMIGD2, and PVR-KIR2DL5. In addition, we have contributed to other immune checkpoints Tim-3, B7-H3, ICOS, PD-L1/PD-1, BTNL2, etc. We are using a variety of approaches (gene knock-out/transgenic mice, humanized mice, patient samples, monoclonal antibodies, single-cell RNA sequencing, structure, imaging, etc) to understand how new immune checkpoints regulate activation and tolerance of T cells and other immune cells. Current emphasis in the lab is placed in the following areas:
1) New immune checkpoints and cancer immunotherapies
2) Autoimmune diseases and immunotherapies
3) metabolic diseases and immunotherapies

Our research has formed scientific foundation and core intellectual property for several start-up drug companies. Two novel immune checkpoint inhibitors from our lab are currently in several phase II and I/II clinical trials in patients with various cancers.

Since 2008 the lab has mentored 49 trainees of MD-PhD or PhD students, postdoctoral fellows, clinical fellows, and visiting scientists. Most of trainees have subsequently moved on to independent careers in academic universities, medical centers, biopharmaceutical industry, and US government agencies.

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