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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!

A handwritten signature in black ink, appearing to read 'Steven A. Porcelli'.

Professor & Chairman
Department of
Microbiology and Immunology

MICROBIOLOGY AND IMMUNOLOGY**FACULTY**
2023-2024

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MICROBIOLOGY AND IMMUNOLOGY

GRADUATE STUDENTS

2023 – 2024

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| Cole, Erin (Goldstein)) | 430-2156 | Forchheimer 408 |
| Corrigan, Devin T. (Zang) | 430-4154 | Forchheimer 408 |
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| DeMouth, Megan (Chandran) | 430-8552 | Golding 403 |
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| Garcia, Sayra (Putterman) | 430-4267 | Forchheimer 701 |
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MICROBIOLOGY & IMMUNOLOGY

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2023 – 2024

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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 Associate Program Director of Einstein's T32 Training Program in Geographic Medicine and Emerging Infections, the Co-Director of Einstein's Global Health Center, and a member of and mentor for the Sub-Saharan African Network for TB/HIV Research Excellence (SANTHE). 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

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

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)

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)

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. 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 impairment and 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. PMID: 31276637

Williams, DW, Calderon, TM, Lopez, L, Carvallo, L, Gaskill, PJ, Eugenin, EA, Moregillo, 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 Across 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. In order 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

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 .

Giroto 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

Chiner-Oms A#, **Berney M#**, Boinett C, Gonzalez-Candelas F, Young D, Gagneux S, Jacobs WR, Parkhill J, Cortes T, Comas I. (Co-first author with equal contribution) Genome-wide mutational biases fuel transcriptional diversity in the *Mycobacterium tuberculosis* complex. **Nature Communications** 10 (1), 1-11

Exploiting the synthetic lethality between terminal respiratory oxidases to kill *Mycobacterium tuberculosis* and clear host infection. Kalia NP, Hasenoehrl EJ, Ab Rahman NB, Koh VH, Ang MLT, Sajorda DR, Hards K, Grüber G, Alonso S, Cook GM, **Berney M*+,** Pethe K*+. **Proceedings of the National Academy of Sciences** (2017) 114, 7426–7431 (+equal contributions)

Mycobacterium tuberculosis in the face of host-imposed nutrient limitation. **Berney M*** & Berney-Meyer L. In **Tuberculosis and the Tubercle Bacillus, Second Edition**, ASM Press. (2017)

OXPHOS as a new target space for tuberculosis: success, failures, and future directions Cook GM, Hards K, Greening C, Heikal A, Dunn E, Nakatani Y, Pethe K, Crick D, **Berney M.** In **Tuberculosis and the Tubercle Bacillus, Second Edition**, ASM Press. (2017)

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, Jacobs WR*. **Proceedings of the National Academy of Sciences** (2015) 112: 10008–10013

Featured with a spotlight article in *Trends in Microbiology*

Full publist:

<https://www.ncbi.nlm.nih.gov/myncbi/michael.berney.1/bibliography/40584568/public/>

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.

Publications

Selected:

Lopez-Scarim J, Nambiar SM, **Billerbeck E**. T cell responses to hepatotropic virus infections in the liver microenvironment. **Vaccines**, March 17, 2023

Raus S, Lopez-Scarim J, Luthy J, **Billerbeck E**. *Hepatic iNKT cells produce type 2 cytokines and restrain antiviral T cells during acute hepacivirus infection.*

Front Immunol. 2022 Sep 9;13:953151. doi: 10.3389/fimmu.2022.953151. eCollection 2022.

Wu X, Dao Thi VL, Huang Y, **Billerbeck E**, Saha D, Hoffmann HH, Wang Y, Silva LAV, Sarbanes S, Sun T, Andrus L, Yu Y, Quirk C, Li M, MacDonald MR, Schneider WM, An X, Rosenberg BR, Rice CM. *Intrinsic immunity shapes viral resistance of stem cells.* **Cell.** 2018 Jan 25;172(3):423-438.e25. doi: 10.1016/j.cell.2017.11.018. Epub 2017 Dec 14.

Trivedi S, Murthy S, Sharma H, Hartlage AS, Kumar A, Gadi S, Simmonds P, Chauhan LV, Scheel TKH, **Billerbeck E**, Burbelo PD, Rice CM, Lipkin WI, Vandergrift K, Cullen JM, Kapoor A. *Viral persistence, liver disease and host response in Hepatitis C-like virus rat model.* **Hepatology.** 2018 Aug;68(2):435-448. doi: 10.1002/hep.29494. Epub 2018 May 21.

Billerbeck E, Wolfisberg R, Fahnoe U, Xiao WJ, Quirk C, Luna JM, Cullen JM, Hartlage AS, Chiriboga C, Ghoshal K, Lipkin IW, Bukh J, Scheel TKH, Kapoor A, Rice CM. *Mouse models of acute and chronic hepacivirus infection.* **Science.** 2017 Jul 14;357(6347):204-208.

Billerbeck E*, Mommersteeg MC*, Shlomai A, Xiao JW, Andrus L, Bhatta A, Vercauteren K, Michailidis E, Dorner M, Krishnan A, Charlton MR, Chiriboga L, Rice CM, de Jong YP. *Humanized mice efficiently engrafted with fetal hepatoblasts and syngeneic immune cells develop human monocytes and NK cells.* **J Hepatol.** 2016 Aug;65(2):334-43.

* equal contribution

Billerbeck E*, Kang YH*, Walker L, Lockstone H, Grafmueller S, Fleming V, Flint J, Willberg CB, Bengsch B, Seigel B, Ramamurthy N, Zitzmann N, Barnes EJ, Thevanayagam J, Bhagwanani A, Leslie A, Oo YH, Kollnberger S, Bowness P, Drognitz O, Adams DH, Blum HE, Thimme R, Klenerman P. *Analysis of CD161 expression on human CD8+ T cells defines a distinct functional subset with tissue-homing properties* **Proc Natl Acad Sci U S A.** 2010 Feb 16;107(7):3006-11

* Equal contribution

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.

Papillomaviruses are 8.0 kb double stranded DNA viruses readily amenable to amplification and sequencing, making this system ideal as a model for DNA virus evolution and identification of pathogenic genetic signatures. Over 200 HPV types exist and further characterization of HPVs infecting the population (i.e., from our large sample repository) have allowed us to explore the virus as a species, characterization of the frequency and heterogeneity of HPV types and variants in the population, and the role of viral evolution in pathogenicity. The lab uses phylogenetic methods and other analytic strategies to test hypotheses about the relationship and characteristics of HPV genomes and disease. Exploration of natural selection of papillomaviruses has led us to the conclusion that the viruses are evolving through complex means yet to be discovered. Our major collaboration with investigators at the National Cancer Institute, NIH has provided an ideal translational team of world-class epidemiologists, biostatisticians and clinical investigators. In combination with evolutionary biologists at the American Museum of Natural History, our integrative group provides a unique prospective for intellectual growth of students that want to “think outside the box”. More recently, we have investigated epigenetic changes to the HPV genome and have demonstrated very significant results on the association of these changes with neoplastic progression. The identification of HPV in specific biological niches has challenged us to explore the microbiome through barcoding and parallel sequencing using Next-Gen methods. We have recently developed the methodologies and computer software to test hypothesis on the influence of the microbiome on cervix cancer development in HPV positive women.

More recently, we have engaged in identifying small molecule inhibitors to HPV oncoproteins and have identified highly active compounds based on the structure of E7.

Other research areas include a human genetic project to identify the gene(s) for hyperhidrosis (excessive sweating). This is a fascinating disorder that is strongly associated with a family history of excessive sweating. There seems to be at least two phenotypes, excessive sweating from the palms and soles, and excessive sweating from the underarms, body, face and groin areas. The analyses of families with this disorder suggest genetic and/or allelic heterogeneity. To date, we have collected over 1500 DNA samples from affected individuals and families. We are in the process of exome-sequencing the coding regions using Next-Gen technologies to identify candidate mutations associated with this disorder.

Lastly, as part of our goal to understand genes and cancer, we have for many years studied the von Hippel-Lindau (VHL) gene that is a driver of kidney cancer. We investigate the function of the VHL protein, in part, an oxygen sensor. Our recent observations indicate that intact VHL is required for primary cilia formation and function in renal cells. We have localized VHL and other proteins known to interact to cilium. Further studies will investigate the function of VHL in the cilium.

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

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

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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.

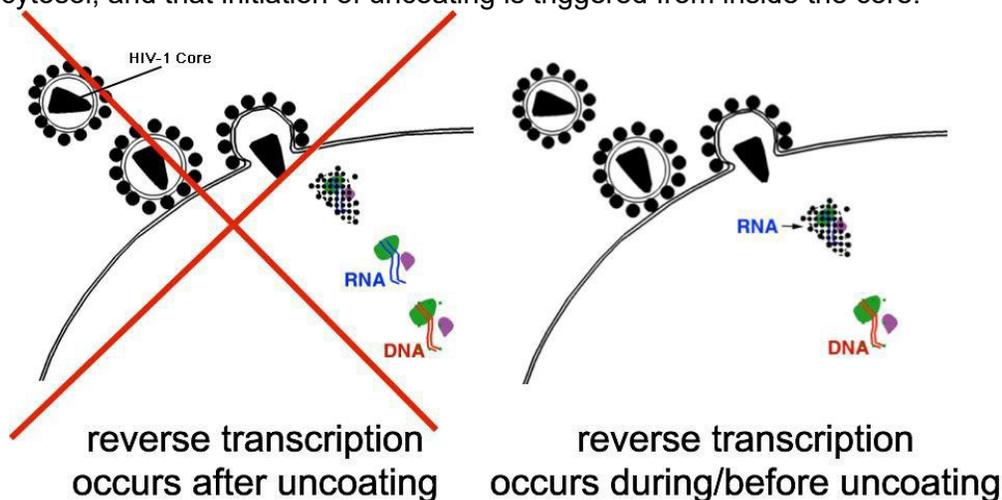


Figure 1. Current model for the occurrence of HIV-1 reverse transcription and uncoating.

Our investigations showed that HIV-1 reverse transcription is completed inside the viral core during/before uncoating. 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 TRIM5 α , 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) TRIM5 α

The HIV-1 restriction factor TRIM5 α 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 TRIM5 α to form higher-order complexes (Diaz-Griffero et al., 2009; 2007b), which is an essential function for the ability of TRIM5 α 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 TRIM5 α 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).

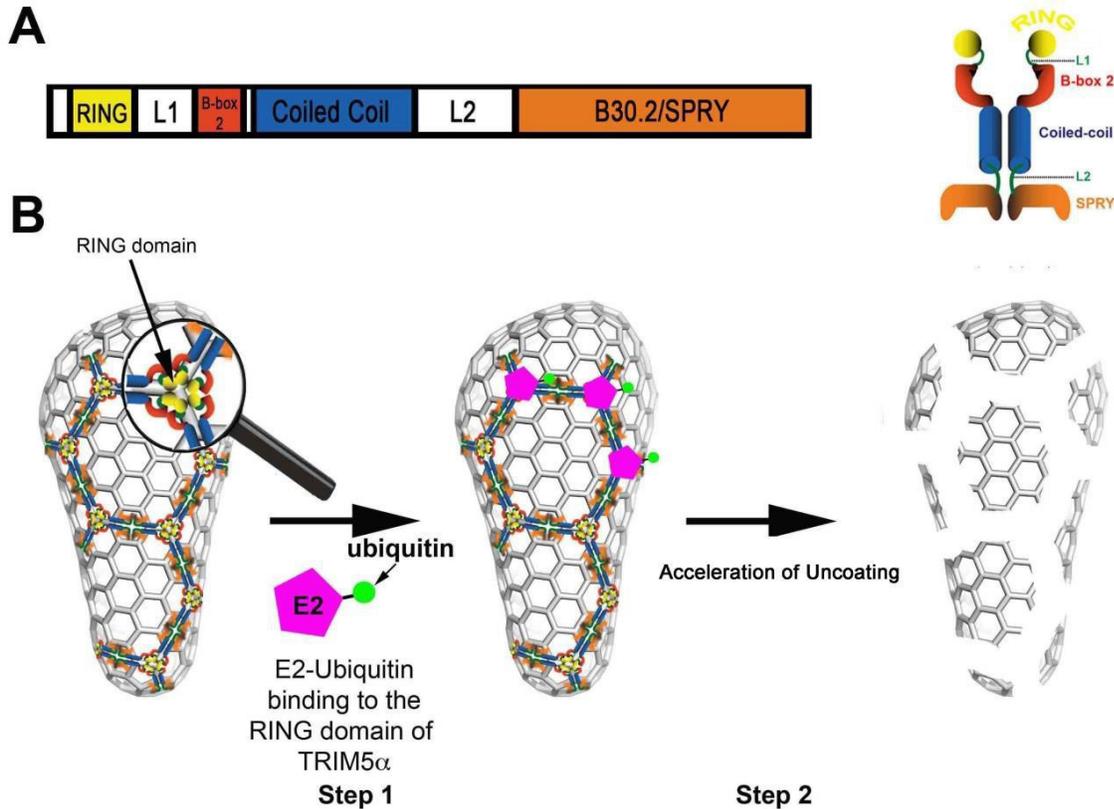


Figure 2. Inhibition of HIV-1 infection by TRIM5 α . (A) The different domains of TRIM5 α are shown, and a small cartoon depicting the TRIM5 α protein is shown on the right side. (B) TRIM5 α proteins assembled forming a hexagonal pattern on the surface of the HIV-1 core, and the RING domain of TRIM5 α 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 TRIM5 α 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.

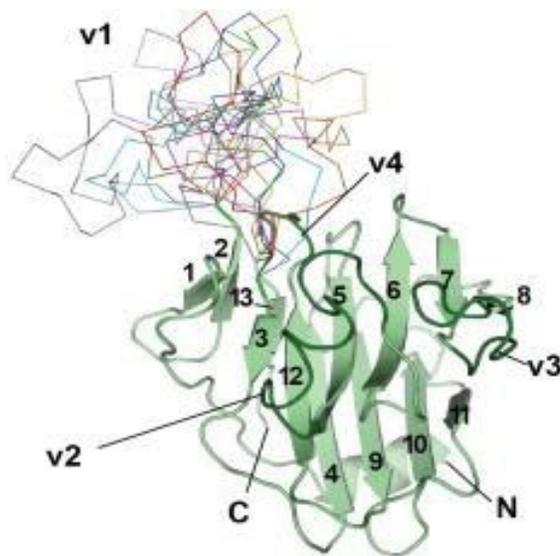


Figure 3. Structure of the PRYSPRY domain of rhesus monkey TRIM5 α . The structure of the PRYSPRY domain is shown. The four variable loops of the protein are indicated as V1, V2, V3 and V4. The V1 loop, which directly interact with the HIV-1 core, exhibited hundred of different conformations, as indicated by the strands in different colors. These observations suggested that the PRYSPRY domain of TRIM5 α 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- α 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.

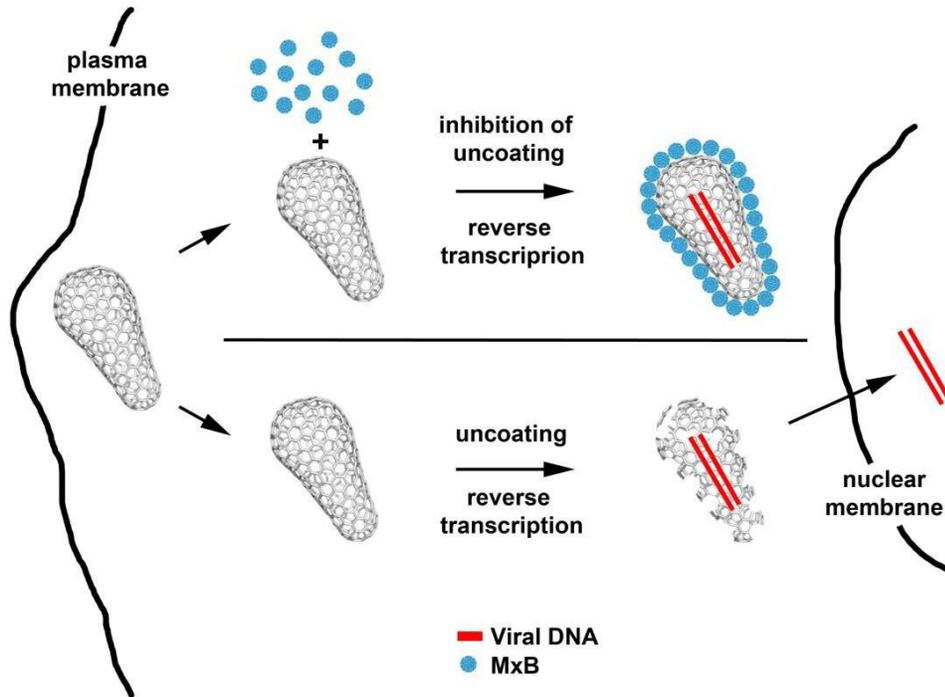


Figure 4. Inhibition of HIV-1 by MxB/Mx2. Our investigations revealed that MxB directly interacts with the HIV-1 core and prevents the uncoating process of HIV-1 terminating infection.

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).

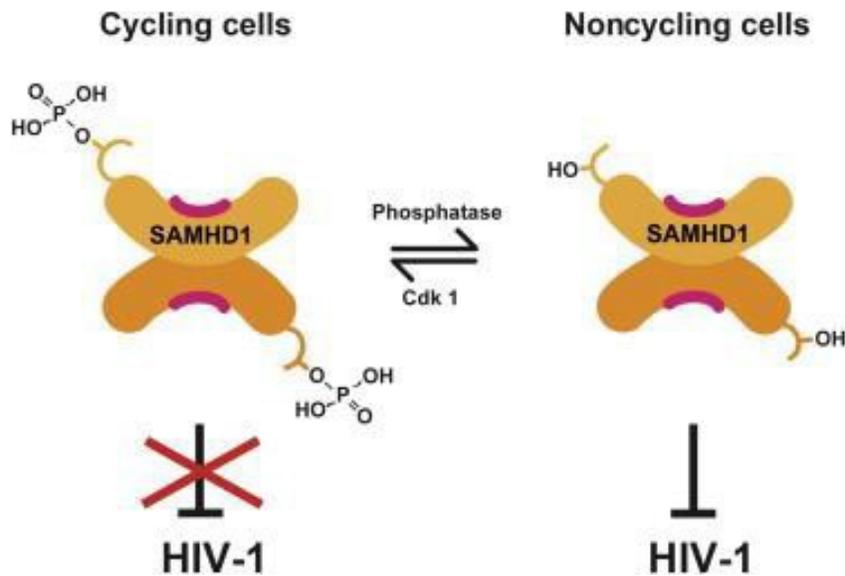


Figure 5. Regulation of SAMHD1 anti-HIV-1 activity by phosphorylation. Our investigations revealed that phosphorylation of SAMHD1 at T592 modulates the ability of this restriction factor to block HIV-1 infection of macrophages.

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.

PUBLICATIONS

(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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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 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 FRANGOIANNIS

Our laboratory studies the cell biological processes and the molecular pathways 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 the molecular signals 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. 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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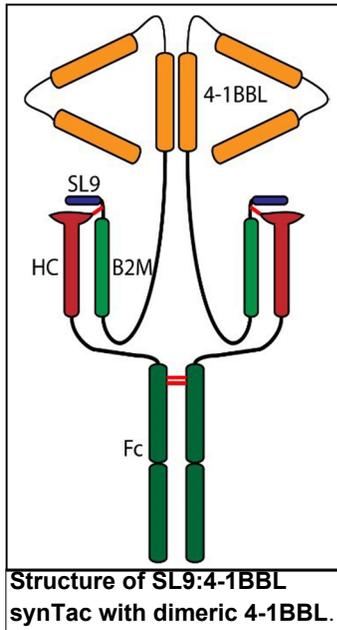
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DR. HARRIS GOLDSTEIN

Our laboratory is utilizing novel molecular, cellular and biochemical approaches to “hack” the human immune system and amplify its activity to enable it to recognize and eliminate reactivated latent HIV-infected T cells (LHITC) and thereby achieve the functional cure of HIV-1 infection. Our lab is part of the NIH-funded *Martin Delaney Collaboratory: Towards an HIV-1 Cure* program established to fulfill President Barack Obama’s pledge to invest in HIV cure research.



The goal of the Delaney program is to unite and synergize the research programs of highly talented investigators to accelerate the development of a safe and scalable cure for HIV. One novel approach we are pioneering is the application of new immune checkpoint modulating biologics, which stimulate the immune system to kill tumor cells and have revolutionized cancer treatment, to amplify the cytotoxic activity of HIV-specific CD8⁺ T cells and increase their capacity to eliminate HIV-infected cells. For this purpose, we are applying synTac (artificial immunological synapse for T-cell activation), a novel class of soluble precision-targeted immunomodulatory biologics developed by the Almo lab. The synTac fusion proteins use a single MHC α and β 2 microglobulin chain containing a defined peptide (sc-pMHC) linked to a costimulatory or cytokine domain to integrate the specificity of antigen-receptor and potency of costimulatory and/or cytokine signaling (see Figure). Antigen specific T cell subpopulations are specifically activated by sc-pMHC binding to its cognate TCR which provides the primary activation signal as well as precisely delivering the costimulatory and/or cytokine signal by the linked costimulatory or cytokine domains. We have validated this approach for HIV by constructing

synTac fusion proteins which target the HLA-A*0201-restricted HIV Gag epitope, SL9, linked to the costimulatory 4-1BBL molecule, SL9:4-1BBL-synTac. The SL9:4-1BBL-synTac specifically bound an SL9-specific CTL clone TCR and stimulated INF- γ and TNF- α secretion and cellular proliferation. We are extending those very promising results by developing synTac-based therapeutics linked to different costimulatory ligands and/or cytokines to identify the optimal costimulatory and cytokine signals required for the specific *in vitro* and *in vivo* activation and expansion of HIV-specific CD8⁺ T cells with the potential to eliminate reactivated LHITC.

Another novel strategy to cure HIV we are investigating and optimizing is amplifying NK cell cytotoxic function by treatment with various structurally enhanced cytokine constructs combined with targeting them to specifically kill reactivated latent HIV-1 infected cells by parallel treatment with molecularly engineered HIV-specific broadly neutralizing antibodies, bispecific antibodies and/or fusion proteins. We are also molecularly engineering the antigen specificity of CD8⁺ T cells to recognize HIV-specific epitopes and generate potent HIV-specific CD8⁺ cytotoxic T lymphocytes (CTLs) by transducing them with lentiviruses expressing the genes encoding the alpha and beta chain of TCRs derived from potent HIV-specific CD8⁺ CTLs. We are further amplifying the cytotoxic capacity of these molecularly engineered HIV-specific CTLs by evaluating which added anti-apoptotic genes or cytotoxic genes added to the TCR-expressing lentiviral vectors improved the their capacity to eliminate reactivated latent infected cells.

Two major impediments prevent the testing of strategies to reduce HIV reservoirs and inhibit viral rebound after the cessation of antiretroviral therapy (ART): 1. The rarity of latent infected cells capable of producing infectious HIV-1; and 2. The difficulty in distinguishing latent infected cells from the majority of infected cells which contain integrated defective proviruses that

cannot produce infectious virus. To evaluate the efficacy of immune system “hacking” strategies to deplete the HIV reservoir, we have established a novel humanized mouse model consisting of highly immunodeficient NSG mice intrasplenically injected with CD4⁺ memory T cells isolated from HIV-infected patients who are virally suppressed by ART treatment (viral loads <50 copies/ml) which include a population of latent HIV-infected cells. We demonstrated that the transplanted HIV reservoir was activated *in vivo* as reported for ART-suppressed individuals during treatment interruption. These mice displayed plasma viremia within 1 week after injection which rapidly rose over the next month. We will be using this mouse model to examine the effects of the aforementioned immune amplification strategies to reduce the HIV reservoir as indicated by elimination of viremia, temporal delay in the onset of the viremia and/or reduction in the amplitude of the viremia. We have also developed another humanized mouse model infectible with an infectious HIV expressing a luciferase reporter that enables us to serially visualize HIV infection in live mice by the intensity of the luciferase signal (see Figure).

The mechanisms by which HIV infection and meth disrupt the blood-brain barrier (BBB), stimulate migration of HIV infected monocytes into the CNS and induce neuroinflammation and the impact of ART on these processes are not fully delineated. This is a highly significant area of research relevant to NIH high priority topics of HIV/AIDS research, understanding the basic biology of HIV pathogenesis causing immune dysfunction and chronic inflammation and addressing the impact of HIV-associated comorbidities including neurological complications. We are also using a novel transgenic mouse we developed, hu-CD4/R5/cT1 mice, which circumvents major entry and transcription blocks preventing murine HIV-1 infection by targeting transgenic expression of human CD4, CCR5 and cyclinT1 genes to CD4⁺ T cells and myeloid-committed cells. These mice develop disseminated HIV-1 infection after intravenous HIV-1 injection and local HIV-1 infection after intravaginal inoculation. We are utilizing these mice to evaluate the *in vivo* efficacy of novel HIV-1 vaccines. In addition, we are using these transgenic mice to evaluate the mechanisms by which co-infection facilitates HIV-1 acquisition and to determine the efficacy of different preventive therapies. By crossing the hu-CD4/R5/cT1 mice with another novel transgenic mouse line we developed, which expresses a full-length HIV provirus that produces infectious HIV, we are investigating the effect of drugs of abuse on disrupting the BBB and facilitating the entry of HIV-infected inflammatory cells into the brain and evaluating the capacity of antibodies to adhesion molecules to prevent the transmigration of HIV-infected inflammatory cells into the brain

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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), measlesvirus (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.

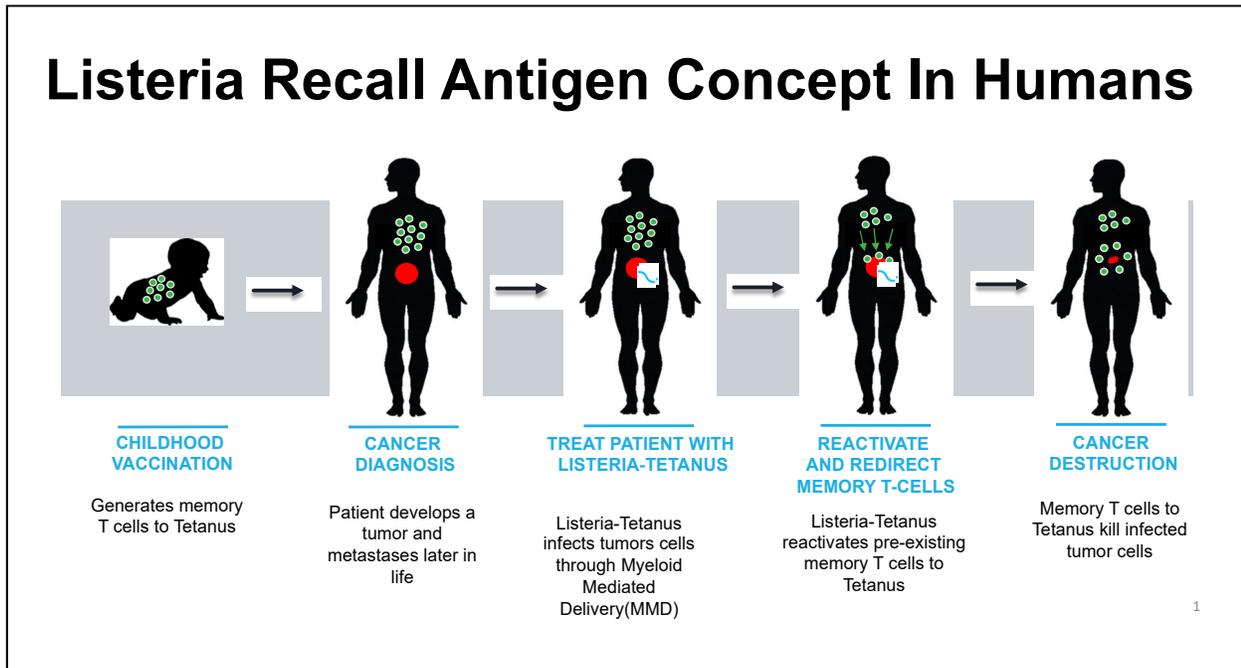
Mechanisms that contribute to the selective survival and multiplication of *Listeria* in the tumor microenvironment

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}Re 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*- ^{32}P by incorporating ^{32}P -phosphorus directly into the *Listeria* during culture. Most likely of the longer half-life of ^{32}P (14 days) than of ^{188}Re (16.9 hrs), *Listeria*- ^{32}P 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 (α GC) into the Listeria bacteria simply during culture. This method was originally developed for mycobacteria. α GC 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 α GC 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, Onolmmunology 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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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 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 vaccine for HSV**. In collaboration with William Jacobs, PhD, the lab developed a paradigm shifting single-cycle HSV-2 vaccine candidate by deleting the immunodominant envelope glycoprotein D (gD), which has been the primary component of prior candidate vaccines. The Herold lab is now pursuing mechanistic studies to determine why this vaccine is different from other candidates that have failed in clinical trials. Primary infection and vaccines that contain gD induce a predominant neutralizing antibody response but have failed to protect in clinical trials. In contrast, the gD deletion virus (Δ gD-2) elicits high titer antibodies that primarily mediate antibody-dependent cell mediated cytotoxicity (ADCC). The vaccine provided 100% protection against vaginal, skin, and neurological infections when mice were challenged with a panel of clinical isolates of HSV-1 and HSV-2, completely prevented the establishment of HSV latency. These antibodies passively protected wild-type but not Fc γ receptor knockout mice. Subsequent studies uncovered a novel immune evasion strategy that may explain why Δ gD-2 (but not natural infection or gD-containing vaccines) elicit ADCC-mediating antibodies. Glycoprotein D binds to an immunomodulatory molecule, HVEM (TNRSF14) on immune cells, which is required for optimal generation of ADCC-mediating antibody responses. Current studies in the lab focus on defining the underlying mechanisms by which HVEM signaling contributes to ADCC, isolating the protective Abs and identifying their targets, developing a new mouse model of recurrent or reactivating HSV and supporting the advancement of the vaccine into the clinic. (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), they 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.

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.**
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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 mycobacteriophages, 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 $\Delta gD-2$, 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 $\Delta gD-2$ 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/>

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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 rhabdoid tumors.

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-mediated 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.

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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, pancreatic, 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 immunosuppression 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 immunofluorescence 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.

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

Microbial populations are dynamic, transactional social networks of paramount importance to human health. The collection of microbes living in and on our bodies (the 'microbiome') is influenced by top-down and bottom-up regulation and these processes are poorly understood. For example, the availability of resources produced by other microbes ('public goods') can inhibit or support the growth of particular microbes (bottom-up). Administering a drug or viral predation can remodel microbial community structure (top-down). Our research program focuses on how microbial populations in the human body respond to perturbations such as diet, disease, and drugs, and how these responses are linked to health outcomes. The overall goal of our work is to empower patients to improve their health via targeted control of their microbiome. Towards this end we study how microbial communities are influenced by top-down and bottom-up regulation with a focus on three main biological questions: 1) How does microbial metabolism of drugs influence treatment outcomes in patients? Here we develop pretherapy analysis protocols to identify patients with high-risk microbiomes; we propose novel prebiotic approaches to influence microbial drug metabolism; and we predict new microbiome/drug interactions. 2) How do interactions between bacteria and archaea at the bottom of the microbial food chain influence access to dietary substrates? We endeavor to increase access to beneficial dietary compounds and we study how aging influences food processing in the gut. 3) How do virus/host interactions influence population-level metabolism in the gut? We predict viral influences on microbiome health and function and we identify new viruses that infect microbial populations in the human gut. Our approaches borrow from many fields and include metabolomics, high throughput genomics, information theory, synthetic chemistry, flow sorting, and imaging. Taken together, my research program forms the foundation of a new field of targeted microbiome manipulation for personalized health care.

Complete Publication List:

<https://scholar.google.com/citations?user=sg7-rm4AAAAJ&hl=en>

Selected Publications and Products:

† Indicates that authors contributed equally to the publication

Xenobiotic metabolism and the human microbiome

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Phage and bacterial genomics and metagenomics

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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*

Microbial pathogens invasion usually triggers potent host immune responses, however efficient protection and pathogen killing require the presence of effector cells and combinations of inflammatory signals that are ill-defined in most infections. Tumor often escape immune responses through a variety of mechanisms including immune suppression.

Our work therefore focuses on precisely defining these events in various settings *in vivo*. Specifically, we investigate (i) the inflammatory signals and related pathways, and innate immune cells that regulate T and innate cell differentiation, and (ii) the cross-talks between memory T cells and innate immune cells. Innate immune cells include monocytes, macrophages, dendritic cells and lymphocytes. We use various models of acute microbial pathogen infections in mice, namely the bacteria *Listeria monocytogenes*, *Streptococcus pneumoniae*, the viruses Vesicular Stomatitis virus and Murine Cytomegalovirus. We study the immune response to the parasite of malaria *Plasmodium* in surrogate mouse models and in human patients. We also investigate the role of poor prognosis mutations found in breast cancer patients on immune cells 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 analyse immune cell expression and epigenetic programming, as well as high end cytometry by time of flight. Overall, the goal of my laboratory is to improve our fine understanding of the factors that orchestrate antimicrobial and antitumoral host protective immune responses *in vivo*. We believe that our work will contribute to better immune cell-mediated preventive and therapeutic vaccination strategies.

PUBLICATIONS

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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 picomolar affinity).

Streptococcus pneumoniae, 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 diphosphomevalonate (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. pneumoniae* 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. pneumoniae* in rich media at ~ 25 µg/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*.

PUBLICATIONS

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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.

Selected Publications

Scherzer R, Greenblatt RM, Merhi ZO, Kassaye S, Lambert-Messerlian G, Maki PM, **Murphy K**, Karim R, Bacchetti P. Use of antimullerian hormone to predict the menopausal transition in HIV-infected women. *Am J Obstet Gynecol* 2017;216:46.e1-11.

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Koedood Zhao M, Wang Y, **Murphy K**, Yi J, Beckerle M, Gilmore T. LIM Domain-Containing Protein Trip6 Can Act as a Coactivator for the v-Rel Transcription Factor. *Gene Expression*. 1999 Sep; 8(1): 207-217.

DR. JOSHUA D. NOSANCHUK

Key Words: fungus, histoplasmosis, cryptococcosis, candidiasis, melanin, wound 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.

PUBLICATIONS

Dr. Nosanchuk has over 300 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 are to 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

Yano M, Coleman JR, Gohil S, Manix C, **Pirofski L**. Antibodies to *Streptococcus pneumoniae* capsular polysaccharide enhance quorum sensing. MBio. Nov 1;2(5). pii: e00176-11. doi: 10.1128/mBio.00176-11, 2011.

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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 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

Im JS, Arora P, Bricard G, Molano A, Venkataswamy MM, Baine I, Jerud ES, Goldberg MF, Yu KOA, Ndonge RM, Howell AR, Yuan W, Cresswell P, Chang YT, Illarionov PA, Besra GS and **Porcelli SA**. Kinetics and cellular site of glycolipid loading control the outcome of Natural Killer T cell activation. *Immunity* 30:888-98 (2009).

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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

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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 determining 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., Duran C., 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. XINGXING ZANG

(Immune Checkpoint and Immunotherapy lab: <https://www.xingxingzanglab.org>)

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.

SELECTED PUBLICATIONS

(@ PhD or MD/PhD students. *corresponding author)

Pulanco MC@, Madsen AT, Tanwar A, Corrigoan DT@, **Zang X***. Recent advancements in the B7/CD28 immune checkpoint families: New biology and clinical therapeutic strategies. *Cellular & Molecular Immunology*, 20:694-713, 2023

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MICROBIOLOGY & IMMUNOLOGY

STUDENT PUBLICATIONS

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