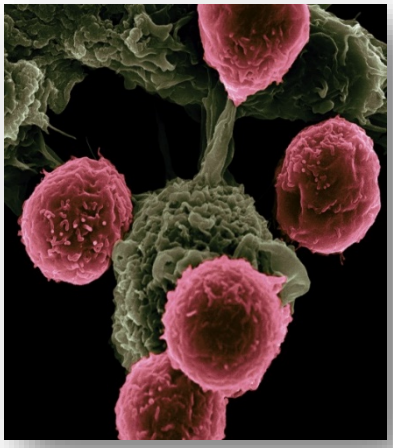
UNIVERSITY of MARYLAND
MARLENE AND STEWART GREENEBAUM
COMPREHENSIVE CANCER CENTER

FEATURES

Tumor Immunology & Immunotherapy

2020 Program Retreat



Co-Leaders:
Xuefang Cao, PhD
Aaron Rapoport, MD

UNIVERSITY of MARYLAND
MARLENE AND STEWART GREENEBAUM
COMPREHENSIVE CANCER CENTER

2020 Tumor Immunology and Immunotherapy Retreat

Virtual Event

Friday, September 18th from 8:45-1:30

Start Time	Presenter	Topic/Title
8:45	Aaron Rapoport & Xuefang Cao	Introductory Remarks
9:00	Aaron Rapoport	New Developments on TCR-T Cellular Immunotherapy for Myeloma
9:20	Svetlana Chapoval	Homology modeling of semaphoring 4A interaction with Plexin B1
9:40	Ryan Pearson	Engineering Nanoparticles for Immunomodulation
10:00	Miroslaw Janowski	Molecular Imaging for Precision Immunotherapy
10:20	Tim Luetkens	Combinatorial strategies to shape therapeutic T cell selectivity
10:40	Darren Perkins	Autocrine Prostaglandin Feedback Restricts STING dependent Inflammatory Responses to Cytosolic DNA
11:00	Nevil Singh	Restoring balance to the T cell multiverse: An IL-4 driving IL-12-family cytokine
11:20	Brian Pierce	High resolution modeling and structure-based design of neoantigen-specific TCRs
11:40	Rania Younis	Histological Immune score and IFN-gamma immune signature in head and neck squamous cell carcinoma
12:00	Xuefang Cao	Beta2-adrenergic signaling in immune homeostasis and reconstitution
12:20	Shyam Kottilil	Eliminating Viral Hepatitis for Cancer Prevention
12: 40	Djordje Atanackovic	Rational design of anti-tumor cellular immunotherapies
1:00	ThermoFisher	Oncomine TCR Beta-LR Assay
1:20	Xuefang Cao	Concluding Remarks

The Tumor Immunology and Immunotherapy (TII) Program Overview

The TII Program at the University of Maryland Marlene and Stewart Greenebaum Comprehensive Cancer Center is dedicated to understanding the immune regulation of malignant disease and translating this knowledge into the development of novel diagnostic and treatment regimens. The program provides a forum to develop interdisciplinary strategies that promote innovative research, create new therapeutic options and reduce the burden of cancer.

The **overall goal** of the TII Program is to develop and implement immune-based strategies to monitor and treat cancer. To achieve this goal, the program focuses on enhancing adaptive and innate antitumor responses and mitigating immunotherapy-related adverse effects. The program includes both full and associate members from University of Maryland Baltimore, University of Maryland College Park and University of Maryland Baltimore County.

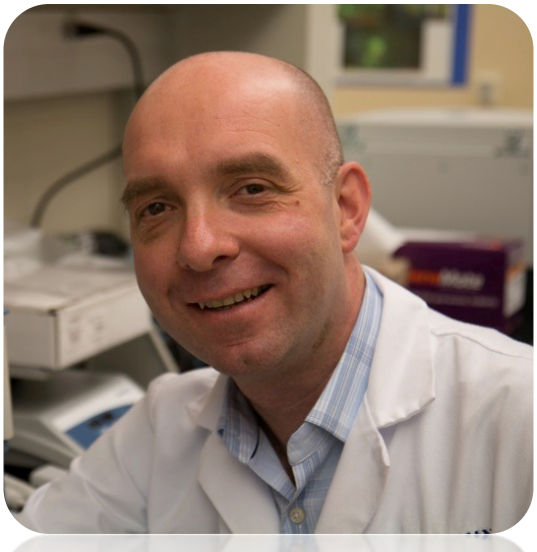
The TII Program's research and clinical endeavors fall under the following themes:

1. Cell-based and regulatory pathway-targeted cancer immunotherapies – Develop cell-based and regulatory pathway-targeted cancer immunotherapies that are capable of reducing or monitoring malignant cell growth.

2. Calibrating immune regulation – Develop strategies to overcome tumor-induced immunosuppression and to mitigate immunotherapy-related adverse effects.

3. Cancer and inflammation – Elucidate the roles for infection and inflammatory responses in cancer development.

TII Members and Research Highlights



Djordie Atanackovic, MD

Professor of Medicine
Director, Cellular and Vaccine Immunotherapy
Medical Director, Fannie Angelos Cellular Therapeutics Laboratory
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Personal Statement

I have a long-standing clinical and research interest in human malignancies and a broad background in tumor immunology and cancer immunotherapy. I started as a postdoctoral fellow at the Ludwig Institute for Cancer Research at Memorial Sloan-Kettering Cancer Center in New York City where I carried out research in tumor immunology focusing on a certain group of tumor-specific proteins, so-called cancer-testis antigens, as potential targets for T cell-based immunotherapies. After I had returned to the University Medical Center Hamburg-Eppendorf in Germany and had founded a translational tumor immunology research group, I decided to perform research on the development of immunotherapeutic approaches for patients with different solid tumors and hematologic malignancies. My group worked on the identification of potential target structures for immunotherapies, the evaluation of the biological function of the given proteins, the analysis of spontaneous anti-tumor immune responses, and the development of cellular and antibody-based approaches for patients suffering from cancer. As PI in multiple clinical trials, I have introduced several of our immunotherapeutic approaches into the clinic.

Projects/Grants

Analysis of B cell and T cell responses in patients with COVID-19 and hematologic malignancies.

CD229 CAR T cell approaches for the treatment of B cell malignancies.

Monitoring of immune responses in multiple myeloma patients treated with the monoclonal anti-CD38 antibody isatuximab.

Recent Publications

Radhakrishnan, S., Luetkens, T., Scherer, S.D., Davis, P., Vander Mause, E.R., 1, Olson, M., Yousef, S., Panse, J., Abdiche, Y., Li, K.D., Miles, R.R., Matsui, W., Welm, A.L., **Atanackovic, D.** (2020) CD229 CAR T cells eliminate multiple myeloma and tumor propagating cells without fratricide. Nature Communications 11: 798

Atanackovic, D., Yousef, S., Shorter, C., Tantravahi, S.K., Steinbach, M., Iglesias, F., Sborov, D., Radhakrishnan, S.V., Chiron, M., Miles, R., Salama, M., Kröger, N., Luetkens, T. (2019) In vivo vaccination effect in multiple myeloma patients treated with the monoclonal antibody isatuximab. Leukemia 34: 317-321

David R. Benavides, MD, PhD

Assistant Professor
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Physiology
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Projects/Grants

K08 NS 114039
"Impact of human anti-NMDA receptor antibodies on glutamate receptor signaling, calcium mobilization, and hippocampal neuronal circuits in autoimmune encephalitis"
The goal of this study is to determine the molecular pathophysiology of anti-NMDAR antibodies on neuronal signaling and network effects in autoimmune encephalitis.
Role: PI

Personal Statement

My current research goal is to determine whether antibodies interacting with neural surface proteins dysregulate intracellular signal transduction cascades and neural circuits. This goal fits within my broader research focus, which is the study of immune regulation of neuronal synaptic structure and function. I have a broad background in neuroscience, with specific training and expertise in protein biochemistry, neuronal signal transduction, primary neuron culture, transgenic animal models, and rodent behavioral analyses. As a graduate student, I employed a multidisciplinary approach to study the role of cyclin dependent kinase 5 (Cdk5) in the regulation of dopamine neurotransmission, glutamate receptor signaling, striatal neuron excitability, and reward-related behavior. During my residency and fellowship training in Neurology and Neuroimmunology, I studied how autoimmune targeting of ionotropic glutamate receptors and other neuronal surface proteins leads to autoimmune encephalitis. As a postdoctoral fellow, I investigated the effects of antibodies to NMDA-type ionotropic glutamate receptors on signal transduction cascades in primary dissociated neuron culture, as well as the use of live cell imaging techniques in neuron culture. I have advanced training in neuroimmunology, molecular neuroscience, and clinical neuroscience.

Recent Publications

1. Metzbower SR, Joo Y, **Benavides DR,** Blanpied TA. Properties of individual hippocampal synapses influencing NMDA-receptor activation by spontaneous neurotransmission. eNeuro 6(3): ENEURO.0419-18.2019. PMCID: PMC6541874.

2. Forrester A, Latorre S, O'Dea PK, Robinson C, Goldwaser EL, Trenton A, Tobia A, Aziz R, Dhawan S, Brennan A, Kurukumbi M, Dong Y, **Benavides DR,** Offurum AI. Anti-NMDA Receptor Encephalitis: A multidisciplinary approach to identification of the disorder and management of psychiatric symptoms. Psychosomatics. 2020 Apr 29. doi: 10.1016/j.psym.2020.04.017. [Epub ahead of print] Review. PubMed PMID: 32507506.

3. Tang GJ, **Benavides DR**. A patient with a history of weight loss presenting with seizures. Neurology. 2020 Jul 10. doi: 10.1212/WNL.0000000000010344. [Epub ahead of print] PubMed PMID: 32651288.

Jonathan S. Bromberg, MD, PhD

Professor of Surgery and Microbiology and Immunology

Vice Chair for Research

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Personal Statement

I have been involved continuously in basic cellular and molecular transplant immunology for over 25 years and have been continuously funded for the entire time. My basic research has always focused on T cell immunobiology, and for more than 15 years has also focused on issues of migration, trafficking, secondary lymphoid organ structure and function, and lymphatic structure and function, and how these processes and structures influence T cell immunity and T cell tolerance in models of cardiac transplantation and pancreatic islet transplantation. I have also maintained an active clinical practice in solid organ transplantation and am thus constantly exposed to the problems of patients and their immune systems, including cellular and humoral rejection, opportunistic infections, chronic viral disease, autoimmune organ failure, and immunosuppression medication side effects. My basic research and clinical interests are especially well suited to complement and inform each other, and to keep each aspect of my professional life current and relevant.

Recent Publications

Xiong Y, Piao W, Brinkman CC, Li L, Kulinski JM, Olivera A, Cartier A, Hla T, Hippen K, Blazar B, Schwab SR, **Bromberg JS**. Sphingosine 1-phosphate (S1P) receptors differentially regulate CD4 T cell migration across afferent lymphatic endothelium. Science Immunology 2019, 4:eaav1263. doi: 10.1126/sciimmunol.aav1263

Piao W, Xiong Y, Famulski K, Brinkman CC, Li L, Wagner C, Saxena V, Simon T, **Bromberg JS**. Regulation of T cell afferent lymphatic migration by targeting LTbR-mediated non-classical NFkB signaling. Nature Comm. 2018, 9:3020. doi: 10.1038/s41467-018-05412-0

Piao W, Xiong Y, Li L, Saxena V, Smith KD, Hippen KL, Williams KM, Paluskievicz C, Willsonshirkey M, Stains JP, Abdi R, Blazar BR, **Bromberg JS**. Regulatory T cells condition endothelial cells for enhanced transendothelial migration. Cell Reports 2020, 30:1052–1062.

Projects/Grants

NIH 1 R01 HL148672; Immunological and functional consequences triggered by the gut microbiota regulate alloimmunity and cardiac transplant outcomes. 1.) Inflammation or suppression is triggered by stimulation of MF and DC innate immune responses by distinct intestinal microbiotas and bacterial species; 2.) Local, regional, and systemic LN remodeling are induced by microbiota-stimulated innate myeloid responses; and 3.) LN remodeling determines lymphocyte trafficking, pro-inflammatory vs. suppressive lymphocyte differentiation, and graft outcome.

NIH 1 R01 AI114496; Lymph Node Structure and Function in Tolerance: Role of Laminins. 1.) Demonstrate that pro-inflammatory LN structures accentuate transplant rejection; 2.) Define mechanisms of stromal cell responses; and 3.) Define specific immunosuppression that results in LN structures that support tolerogenic immune responses.

NIH 1P01AI153003; Lymph nodes at the crossroads of allo immunity and regulation: Reshaping lymph node stroma for transplant tolerance. 1.) Define the role of stromal cells in controlling the balance of LAMA4 and LAMA5 during alloimmune responses; 2.) Define the role of LTβR activation of stromal cells as a key pathway in regulating formation of LAMA5; and 3.) Use targeted nanodelivery of costimulatory molecule anti-CD40L mAbs and anti-LAMA5 Abs to the LN to promote tolerance.

Xuefang Cao, PhD

Associate Professor
Microbiology and Immunology

Co-Leader, Tumor Immunology & Immunotherapy Program (TII)

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Personal Statement

My scientific interests have been directed toward understanding the complexities of T cell biology and how T cells contribute to tumor immunity and transplantation immunity. My long-term goal is to develop immune-based therapies that are safe and effective for cancer patients. To this end, my lab focuses on investigating the cellular and molecular mechanisms governing T cell differentiation, activation, and effector function. Specifically, we are interested in the co-stimulatory and co-inhibitory signals, sympathetic neurotransmitters, and cytotoxic pathways that are involved in the reciprocal interaction among T cells, other immune cells, and tumor cells. Currently we are studying cancer patients and mouse models, including syngeneic tumor models and allogeneic hematopoietic cell transplantation (allo-HCT), to develop T cell-based and regulatory pathway-targeted cancer immunotherapies. In the setting of allo-HCT, we are designing and testing novel strategies that can control graft-versus-host disease (GVHD) while preserving the beneficial graft-versus-leukemia (GVL) effect.

Projects/Grants

CD27/CD70 Mediated Negative Regulation of Inflammatory T Cell Responses
R01 HL135325, Role: PI
Major goals are to study the mechanisms by which CD27/CD70 signaling inhibits allogeneic inflammatory T cell response and to develop innovative strategies targeting CD27/CD70 that can control GVHD and improve the quality of life for allo-HCT patients.

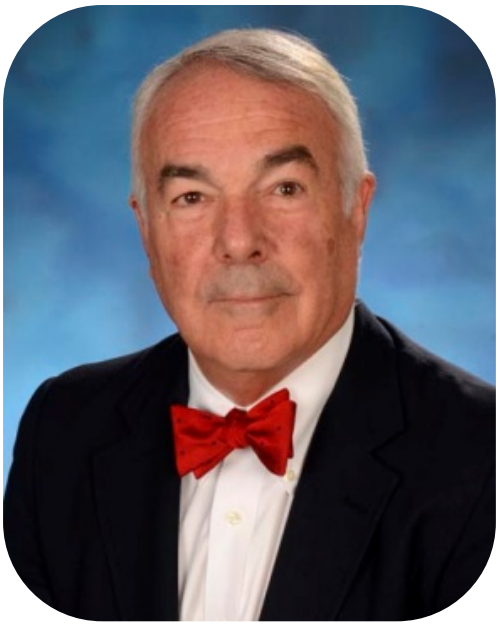
Targeting Granzyme B to Separate GVH From GVL Responses
R01 CA184728, Role: PI
Major goals are to study the mechanisms of granzyme B-dependent separation of graft-versus-host (GVH) and graft-versus-leukemia (GVL) responses and to develop innovative strategies targeting granzyme B to enhance GVL effect while alleviating GVHD.

Recent Publications

Takaaki Oba, Toshifumi Hoki, Takayoshi Yamauchi, Tibor Keler, Henry C. Marsh, **Xuefang Cao,** and Fumito Ito. A critical role of CD40 and CD70 signaling in Batf3 dendritic cells in expansion and antitumor efficacy of adoptively transferred tumor-specific T cells. J Immunol. 2020, In Press

Mohammadpour H, Sarow JL, MacDonald CR, Chen GL, Qiu J, Sharma UC, **Cao X,** Herr MM, Hahn TE, Blazar BR, Repasky EA, McCarthy PL. β2-adrenergic receptor activation on donor cells ameliorates acute GvHD. JCI Insight. 2020 May 21:137788. PMID: 32437333

Paluskievicz CM, **Cao X**, Abdi R, Zheng P, Liu Y, Bromberg JS. T Regulatory Cells and Priming the Suppressive Tumor Microenvironment. Front Immunol. 2019 Oct 15;10:2453. PMID: 31681327



Alan S. Cross, MD
Professor of Medicine
Center for Vaccine Development
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Personal Statement

As an infectious diseases physician I have had a long-standing interest in infections in the immunocompromised host and sepsis. I have developed vaccines against Gram-negative bacterial pathogens as well as other immunomodulatory strategies. In addition, I am studying the efficacy of CD28 and B-7 mimetic peptides for their ability to attenuate the cytokine storm that occurs secondary to excessive inflammation. These strategies may be particularly useful in combatting infections due to antimicrobial resistant infections (i.e. "superbugs"). My laboratory also studies the role of glycobiology, particularly sialic acid modulation, in the innate and adaptive immune response. We have published that removal of cell surface sialic acid by exogenous and/or endogenous sialidases primes the immune response to respond robustly.

Projects/Grants

In collaboration with Astellas Pharmaceuticals in Japan and Affinivax LLC in Cambridge, MA we are developing a multivalent vaccine against *Pseudomonas aeruginosa* and *Klebsiella pneumonia* using a novel vaccine platform. In a separate project I have been examining the therapeutic potential of bovine colostrum on both gastrointestinal infections and intestinal inflammation. Under a DoD grant we are studying the ability of CD28- and B-7 mimetic peptides to protect against burn wound sepsis due to Klebsiella and Pseudomonas infection.

Recent Publications

Choi M, Tennant S, Simon R, **Cross A**. Progress towards the development of Klebsiella vaccines. Expert Rev Vaccines 2019 Jul; 18(7): 681-91. Epub 2019 Jun 28 PMID: 31250679

Choi M, Hegerle N, Nkeze J, et al The diversity of lipopolysaccharide (O) and capsular polysaccharide (K) antigens in invasive Klebsiella pneumoniae in a multi-country collection. Front Microbiolo (in press 2020)

Lillehoj E, Guang W, Hyun S, et al. NEU1 desialylates the MUC1 ectodomain to release a decoy receptor that protects against lethal Pseudomonas aeruginosa lung infection" . J Biolog Chem 2019 Jan11; 294(2):662-678. PMID: 30429216.

Saurabh Dahiya, MD FACP

Assistant Professor
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Personal Statement

Saurabh Dahiya, MD, FACP is an Assistant Professor of Medicine in the Division of Hematology and Oncology at the University of Maryland School of Medicine. Dr. Dahiya is a triple board-certified physician in Internal Medicine, Hematology and Medical Oncology. His clinical focus includes the care of patients undergoing Allogeneic or Autologous Hematopoietic Stem Cell Transplantation and cellular immunotherapy for hematologic conditions. His research interests include translational research and conducting clinical trials in the fields of Adoptive T-cell therapy, such as CAR-T cell therapy, and stem cell transplantation.

Projects/Grants

Phase I, First-in-Human, open-label clinical trial evaluating safety, efficacy and feasibility of Adapter CAR T cells in combination with a Tag in subjects with relapsed or refractory CD 20+ B-Cell-Lymphoma (B-CL).
Immunophenotyping of the Cells of the Innate and Adaptive Immune System in SARS-CoV-2 Infection

Recent Publications

Holtzman NG, Xie HM, Bentzen S, Kesari V, Bukhari A, El Chaer F, Lutfi F, Siglin J, Hutnick E, Gahres N, Ruehle K, Ahmad H, Shanholtz C, Kocoglu H, Badros A, Yared JA, Hardy NM, Rapoport AP, **Dahiya S**. Immune Effector Cell-Associated Neurotoxicity Syndrome (ICANS) after CD19 Chimeric Antigen Receptor T-cell Therapy for Large B-cell Lymphoma: Predictive Biomarkers and Clinical Outcomes. Under review in Neuro-Oncology.

Siglin J, Bukhari A, Lutfi F, Holtzman NG, Shanholtz C, Yared JA, Hardy NM, Rapoport AP, **Dahiya S**. C-reactive protein: not always a reliable marker of ongoing cytokine release syndrome in CAR-T therapy following IL-6 blockade. Leuk Lymphoma. 2020 Apr 28:1-3.

Bukhari A, El Chaer F, Koka R, Singh Z, Hutnick E, Ruehle K, Lee ST, Kocoglu MH, Shanholtz C, Badros A, Hardy N, Yared J, Rapoport AP, **Dahiya S**. Rapid relapse of large B-cell lymphoma after CD19 directed CAR-T-cell therapy due to CD-19 antigen loss. Am J Hematol. 2019 Oct;94(10):E273-E275.

Magali Fontaine, MD, PhD

Professor
Pathology
Medicine
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Personal Statement

My current position is Professor of Pathology and Medicine at the University of Maryland School of Medicine. Previously, I served as Assistant Professor and Associate Medical Director of the Transfusion Service at the Stanford University Medical Center. At both institutions, my interests and contributions have been focused on both cellular therapies and transfusion medicine in the prevention of transfusion adverse events. My laboratory studies the activation profiles of blood leukocyte subsets, in patients with or without a history of transfusion reactions. Platelet and red blood cell interactions are explored as playing a role as well in regulating leukocyte activation. My contribution in cellular therapy lies at the intersection of transfusion medicine and transplantation. Novel cellular therapies are being developed worldwide, such as pancreatic islet transplantation for patients with type 1 diabetes; CAR-T cells, NK cells and dendritic cell-based cancer immunotherapies as well as mesenchymal stromal cells (MSCs) to treat inflammatory diseases. My laboratory is participating in an international inter-laboratory study to evaluate the reproducibility of growing various types of immune cells such as MSCs, and to test their immunomodulatory properties.

Projects/Grants

Center of Excellence in Regulatory Science and Innovation (CERSI-FDA) award To evaluate efficacy of pathogen inactivation strategies for platelet transfusion.

UMB ICTR Voucher Program Award Investigating the role of platelet-leukocyte aggregates in transfusion adverse events.

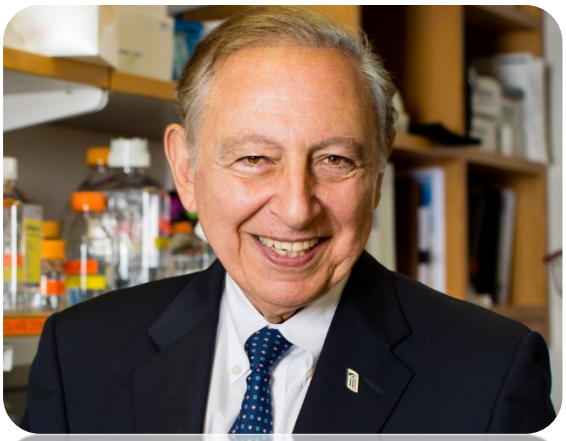
MSCRF Pilot innovative award (T. Kingsbury PI) Leveraging novel SIX 1 transcription factor network interactions to stimulate human erythropoiesis.

Recent Publications

Fontaine MJ. Role of Complement in patients with autoimmune hemolytic anemia and platelet transfusion refractoriness. *Trans Clin Biol*. 2019, 26(3):152-154

Fontaine MJ, Selogie E, Stroncek D, McKenna DH, Szczepiorkowski ZM, Takanashi M, Garritsen H, Girdlestone J, Reems JA, Biomedical Excellence for Safer Transfusion (BEST) Collaborative.Variations in Novel Cellular Therapy Products Manufacturing. *Cytotherapy* 2020 Jun;22(6):337-342

Colin M, Jackson B, **Fontaine MJ**. Tools for Rapid Analysis of Blood Usage and Inventory During the COVID-19 Pandemic. *Transfusion* 2020. https://doi.org/10.1111/trf.15996



Robert C. Gallo, MD

Homer & Martha Gudelsky Distinguished Professor in Medicine
Professor, Microbiology and Immunology
Co-Founder & Director, Institute of Human Virology at the University of Maryland School of Medicine
Co-Founder & International Scientific Advisor, Global Virus Network
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Projects/Grants

Developing candidate HIV vaccines now in phase 2 trials

Studies of the genomic changes in SARS-CoV-2

The role of the innate immune system in stopping the pandemic. Specifically the use of "live" attenuated viral vaccines such as Oral Polio Vaccine, Measles-Mumps-Rubella (MMR) and BCG.

NIH: Durable Antibody Protection Against HIV

Personal Statement

Dr. Gallo is recognized internationally for his co-discovery of HIV as the cause of AIDS. As a biomedical research scientist, he since has spent much of his career working to eliminate AIDS and other viral chronic diseases. In the early 1980s, Gallo and his team also pioneered the development of the HIV blood test, which enabled healthcare labors to screen for the AIDS virus for the first time, leading to a more rapid diagnosis while simultaneously protecting patients receiving blood transfusions. His research also helped physicians develop HIV therapies to prolong the lives of those infected with the virus. His 1996 discovery that a natural compound known as chemokines can block the HIV virus and halt the progression of AIDS was hailed by *Science* magazine as one of that year's most important scientific breakthroughs.

Before the AIDS epidemic, Gallo was the first to identify a human retrovirus and the only known human leukemia virus—HTLV—one of few known viruses shown to cause a human cancer. In 1976, he and his colleagues discovered Interleukin-2, which is a growth-regulating substance now used as therapy in some cancers and even AIDS. Then in 1986, he and his group discovered the first new human herpes virus in more than 25 years (HHV-6), which was later shown to cause an infantile disease known as Roseola.

Today, Dr. Gallo's work continues at the Institute of Human Virology (IHV), an institute of the University of Maryland School of Medicine that Dr. Gallo helped found in 1996. IHV is the first virology center of its kind, combining the disciplines of research, patient care and prevention programs in a concerted effort to speed the pace of progress. In 2011, Gallo co-founded the Global Virus Network to position the world to rapidly respond to new or re-emerging viruses that threaten mankind, to achieve collaboration among the world's leading virologists, and to support next-generation training. As the IHV and GVN address the current pandemic, Dr. Gallo and his colleagues are prominently proposing the oral polio vaccine as a stopgap for the current pandemic before we obtain, if ever, an effective, proven safe, durable vaccine that is ready for distribution and that stimulates the adaptive immune system. Dr. Gallo strongly believes this could have and should have been Plan A while other vaccines are under development.

Recent Publications

1. Chumakov, K., Benn, C.S., Aaby, P., Kottilil, S., and **Gallo, R.C.** (2020). The use of non-specific protective effects of live vaccines to prevent COVID-19. *Science Journal*. June 2020

2. Benedetti F, Snyder GA, Giovanetti M, Angeletti S, **Gallo RC**, Ciccozzi M, Zella D. *(2020). Emerging of a SARS-CoV-2 viral strain with a deletion in nsp1.* (2020). *Journal of Translational Medicine 2020.*

3. Pachetti M, Marini B, Benedetti F, Giudici F, Mauro, E, Storici P, Masciovecchio C, Angeletti S, Ciccozzi M, **Gallo RC**, Zella D, Ippodrino R (2020). Emerging SARS-CoV-2 mutation hot spots include a novel RNA-dependent-RNA polymerase variant. *Journal of Translational Medicine* 2020.

Alfredo Garzino-Demo, PhD

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Personal Statement

My primary interest is to investigate how infectious diseases affect cancer development and vice versa. In the past, my research was focused on how HIV infection can lead to increased occurrence of certain cancers, which are usually more aggressive in HIV positive patients than in seronegative patients. Our hypothesis was that HIV protein can induce angiogenesis, creating a microenvironment which favors tumor growth and metastasis. The recent COVID-19 pandemic has inspired a shift in our studies, and we are now interested in how the immune response to COVID-19 can be shaped by cancer.

Projects/Grants

Chronic Myeloid Leukemia (CML) is a cancer that could have a unique relationship with COVID-19, including the fact that high levels of IL-6 are observed in both diseases, and Tyrosine kinase inhibitors (TKI), targeting the protein resulting from the BCR-Abl1 rearrangement, can inhibit Coronaviruses and are being evaluated against SARS-CoV-2. In addition, it has been reported that TKI treatment, because of off-target inhibition of Bruton's tyrosine kinase and other effectors of B cell intracellular signaling, results in lower frequencies of memory B cells and B cell responses in CML. Therefore, while TKI treatment may have a beneficial effect in the acute phase of COVID-19, the impairment in B cell responses may be detrimental to long-term protection afforded by memory B cells. At present, very little is known on how CML and COVID-19 may affect each other, and how therapy could further alter disease outcome; and even less is known on the induction of antibodies, their duration, and their effector function. We hypothesize that CML patients in remission after TKI treatment have less severe symptomatology in the acute phase of COVID-19; however, TKI treatment may result in less durable antibody responses, both neutralizing and non-neutralizing.
We are collaborating with a multi-center CML cohort, and with Dr. Emadi at UMB, who is the PI of a phase III clinical trial to test Imatinib in COVID-19 subjects. At our Institute, we have state of the art technology, and high-throughput assays to analyze and identify antibodies, their effector activities, and identify precursor B cells producing them. Comparing CML patients to non-cancer controls, we will be able to identify and quantify differences in production of antibodies and effector activities against SARS-CoV-2. We will conduct the same analyses on samples obtained from the Phase III clinical trial of Imatinib, comparing patients treated with the test drug Vs. patients from the placebo group.

Nancy M Hardy, MD, MA, FACP

Associate Professor
Medicine
Department of Medicine
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Projects/Grants

Development of a cGMP cell therapy manufacturing facility at UMSOM.
STTR Grant, NIH/CDC/FDA: R42: Microfluidic CAR-T Cell Processing Device. PI: Curt Civin, MD (UMSOM/Stem Cell Institute).
NIH R01: Inhibitory CD27/CD70 Donor T Cell Interactions in GVHD. PI: Xuefang Cao, MD, PhD.

Personal Statement

My research focuses on clinical and translational development and characterization of cellular immunotherapies for cancer. With comprehensive clinical training in medical oncology and host-defense oriented infectious diseases, as well as laboratory postdoctoral training in basic experimental transplantation and immunology, I have unique translational research expertise in cancer immunotherapy. While at the National Cancer Institute (NCI), I explored ways of augmenting the allogeneic immune response after stem cell transplantation (SCT) to treat cancer relapse. This led to the identification of donor-derived tumor infiltrating lymphocytes and their ex-vivo expansion and cell therapy for tumor progression after SCT, and piloting radiation-enhanced cell therapy to boost tumor immune responses in vivo. Collaborations within the NCI investigated allograft engineering, and led to the establishment of chimeric antigen-receptor (CAR) T-cell therapies targeting CD19 and BCMA for B-cell malignancies and multiple myeloma, respectively. In my current position, I directly oversee key aspects of cell therapy at the University of Maryland Greenebaum Comprehensive Cancer Center (target-cell collection by apheresis; cell processing; patient administration). I bring my translational immunotherapy expertise to partnerships with scientific investigators in academics and industry to develop cell processing innovations and identify therapeutic targets for emerging engineered T-cell therapeutics. For example, I am collaborating with scientists from the University of Maryland Center for Stem Cell Biology & Regenerative Medicine and physicists & engineers at Princeton University on scale-up and commercialization of a novel microfluidics technology which permits rapid and gentle target-cell enrichment, moving this diagnostics-scale technology to clinical scale to improve manufacturing of cell therapy. My active clinical research encompasses all phases of cell therapy trials with investigators across the campus and around the world, including CD24Fc for GVHD Prevention, pioneered by UMSOM investigators; CD19 CAR-T cells, genetically modified T cells expressing enhanced T cell receptors specific for tumor-associated antigens; and novel therapies for graft-vs-host disease.

Recent Publications

Holtzman NG, Xie H, Bentzen S, et al. Immune Effector Cell-Associated Neurotoxicity Syndrome after Chimeric Antigen Receptor T-cell Therapy for Lymphoma: Predictive Biomarkers and Clinical Outcomes [published online ahead of print, 2020 Aug 5]. *Neuro Oncol*. 2020;noaa183. doi:10.1093/neuonc/noaa183.

Solomon SR, Martin AS, Zhang MJ, et al. Optimal Donor for African Americans with Hematologic Malignancy: HLA-Haploidentical Relative or Umbilical Cord Blood Transplant [published online ahead of print, 2020 Jul 7]. *Biol Blood Marrow Transplant*. 2020;S1083-8791(20)30406-7. doi:10.1016/j.bbmt.2020.06.029.

Siglin J, Bukhari A, Lutfi F, et al. C-reactive protein: not always a reliable marker of ongoing cytokine release syndrome in CAR-T therapy following IL-6 blockade. *Leuk Lymphoma*. 2020;61(9):2280-2282. doi:10.1080/10428194.2020.1757667.

Bret A. Hassel, PhD

Professor of Microbiology and Immunology, University of Maryland School of Medicine
Director, Graduate Program in Molecular Microbiology and Immunology
Director, Nathan Schnaper Intern Program in Translational Cancer Research
Financial Sustainability Co-Chair, UMB CURE Scholars Program
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Personal Statement

My research interests for over 30 years have centered on dissecting the mechanisms by which the endonuclease RNase-L mediates innate immune and tumor suppressor functions, and how these can be targeted for clinical applications. My current professional activities focus on graduate training and education as Director of the *Molecular Microbiology and Immunology* graduate program. Most recently, my roles in UMGCCC Education and Training have expanded through the development of six new NIH-funded programs on which I serve as PI or co-I. These serve middle/high school (*UMB CURE, CURE Connections*), undergraduate (*Nathan Schnaper Intern Program [NSIP],* BUILDII *ASCEND*), post-baccalaureate (*STAR-PREP*) and Master's degree (*Bridges to the Doctorate*) students to form a cancer-focused STEM education 'pipeline'. An overarching goal of these programs is to inspire students, including those from underrepresented groups, to pursue careers in research and healthcare and increase diversity in the biomedical workforce.

Projects/Grants

The Nathan Schnaper Summer Intern Program in Translational Cancer Research.
The goal of this grant is to inspire and train the next generation of cancer researchers and physicians. Mentored research, educational, and clinical training components comprise a robust program for a talented group of undergraduate interns from across the United States.

Bridges to the Doctorate: A Partnership Between TU and UMSOM
The overarching goal of this grant is to provide a supportive minority-focused training program that employs the extensive research resources and expertise at UMSOM and TU. In this program, underrepresented minority (URM) students gain critical research and professional skills while completing their master's degree at TU. B2D training prepares students for the successful transition from master's to doctoral programs and completion of the doctorate at UMSOM.

Recent Publications

Ezelle HJ, Geiman T, Schnaper LA, Cullen KJ, Lapidus RS, **Hassel BA.** A Translational Approach to Cancer Research, Education and Training. *J Cancer Educ.* 2020 Jan 6 doi.org/10.1007/s13187-019-01675-3. PubMed PMID: 31907826; NIHMSID 1611875

Miroslaw Janowski, PhD

Associate Professor
Department of Diagnostic Radiology and Nuclear Medicine
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Personal Statement

My research interests include using molecular imaging to guide neurointerventions. It includes delivery of a variety of classes of therapeutic agents such as proteins (antibodies, nanobodies, and others), nanoparticles (dendrimers, iron oxide), extracellular vesicles (EVs) and cells (stem and immune cells). I am using several imaging techniques including nuclear medicine (PET imaging), MRI, bioluminescence, fluorescence and others.

Projects/Grants

Image-Guided, Intra-Arterial Delivery of Human MSC-Derived Extracellular Vesicles for Treatment of Ischemic Stroke

Recent Publications

Andrzejewska A, Dabrowska S, Nowak B, Walczak P, Lukomska B, **Janowski M.** Mesenchymal stem cells injected into carotid artery to target focal brain injury home to perivascular space. Theranostics. 2020 May 17;10(15):6615-6628

Lesniak WG, Chu C, Jablonska A, Behnam Azad B, Zwaenepoel O, Zawadzki M, Lisok A, Pomper MG, Walczak P, Gettemans J, **Janowski M.** PET imaging of distinct brain uptake of a nanobody and similarly-sized PAMAM dendrimers after intra-arterial administration. Eur J Nucl Med Mol Imaging. 2019 Aug;46(9):1940-1951.

Zawadzki M, Walecki J, Kostkiewicz B, Kostyra K, Pearl MS, Solaiyappan M, Walczak P, **Janowski M.** Real-time MRI guidance for intra-arterial drug delivery in a patient with a brain tumor: technical note. J Neurointerv Surg. 2019 Aug;11(8):e3.

Christopher M. Jewell, PhD

Minta Martin Professor of Engineering
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Personal Statement

Christopher M. Jewell is the Minta Martin Professor of Engineering in the Fischell Department of Bioengineering at the University of Maryland – College Park. Dr. Jewell is also a faculty member in the Department of Microbiology and Immunology at the University of Maryland – Baltimore, as well as a Research Biologist with the United States Department of Veterans Affairs at the VA Maryland Healthcare System. Dr. Jewell's research spans biomaterials and immunology to study immune function for therapeutic vaccines targeting cancer and autoimmunity. He earned his PhD in Chemical Engineering from the University of Wisconsin and B.S. degrees in Molecular Biology and Chemical Engineering from Leigh University. After his PhD, Dr. Jewell worked as a consultant at the Boston Consulting Group in the Healthcare Practice of the New York Office. Dr. Jewell completed his postdoctoral training at MIT and Harvard. He is the recipient numerous awards, including the Presidential Early Career Award for Scientists and Engineers (PECASE) awarded by the White House. Dr. Jewell is also a Fellow of the American Institute for Medical and Biological Engineering (AIMBE).

Projects/Grants

Harnessing biomaterials to study the link between local lymph node function and systemic tolerance
R01 EB026896 (NIH, NIBIB), PI: Christopher M. Jewell
***Project selected for NIH Concept-to-Clinic C3i Commercialization Program

Programming immune function through modular assembly of polyionic immune signals
R01 EB027143 (NIH, NIBIB); PI: Christopher M. Jewell

Improving multiple sclerosis patient quality of life using microneedle patches to deliver MS Drugs
R01 AI144667 (NIH, NIAID); PI: Christopher M. Jewell

Recent Publications

G. M. Lynn, R. Laga, and C. M. Jewell*, "Induction of anti-cancer T cell immunity by in situ vaccination using systemically administered nanomedicines" *Cancer Letters* **2019**, *459*, 192-203.

H. B. Eppler and C. M. Jewell, "Biomaterials as tools to decode immunity" *Advanced Materials* **2019**

G. M. Lynn, et al. "Peptide-TLR-7/8 agonist conjugate vaccines chemically programmed for nanoparticle self-assembly enhance CD8 T cell immunity to tumor neoantigens" *Nature Biotechnology* **2020**, 38, 320-332.

Dhan V. Kalvakolanu, M.S., Ph.D.
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Personal Statement

My research interests are in the area of Molecular Cancer Biology, cytokine induced innate immunity, Signal transduction, autophagy, and transcriptional regulation of gene expression. My seminal contributions include the discovery of GRIMs, a novel group of tumor suppressor genes; novel cytokine inducible gene regulatory elements, their cognate transcription factors and pathways that control them. We identified a nuclear genome coded mitochondrial tumor suppressor, GRIM-19, and its interacting partners, functionally inactivating somatic mutations, loss of expression in primary human tumors. We have also developed conditional knockout mouse models that allow the study of tumor suppressors and oncogenes. Before the emergence of whole genome sequence, my lab contributed several novel genes and their sequences to GenBank. We were also one of first group to apply genome-wide expression knockdown technologies before the description of whole genome sequences and RNAi technology. I am the Editor-in-Chief of Cytokine, a journal dedicated for the study of cytokine actions. I am also an editor for the JBC, Cytokine and Growth Factor Reviews, and the Journal of Interferon and Cytokine Research.

Projects/Grants

1R43CA228813-01A1 Targeting galectin-3 to overcome drug resistance in metastatic prostate cancer therapy

1R41CA217438-01A1 GRIM-19 for Head and Neck

Recent Publications

1. Zhao, Y., Liu, H., Xu, L., Guo, B., **Kalvakolanu, D. V.,** Liu, X., Hu, J., Zhang, D., Sun, Y., Zhang, L., Xu, D. & Zhao, X. (2018) Synergistic Suppression of Melanoma Growth by a Combination of Natural dsRNA and Panaxadiolsaponins. J Interferon Cytokine Res 38, 378-387.

2. Duan, Y., Dong, Y., Hu, H., Wang, Q., Guo, S., Fu, D., Song, X., **Kalvakolanu, D. V.** & Tian, Z. (2019) IL-33 contributes to disease severity in Psoriasis-like models of mouse. Cytokine 119, 159-167.

3. Xu, Y., Wang, X., Guo, B., Wang, D., **Kalvakolanu, D. V.,** Chen, X., Tang, J., Zhang, L. & Yang, Q. (2019) Nonviral Delivery of GRIM-19 Gene Inhibits Tumor Growth with Reduced Local and Systemic Complications. Hum Gene Ther 30, 1419-1430.

Achsah D. Keegan, PhD

Professor of Microbiology and Immunology
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Personal Statement

Inflammatory cells and the soluble factors they produce are essential mediators in the tumor microenvironment. Cells of the monocyte-macrophage lineage are found in large numbers in tumors. These tumor associated-macrophages (TAMS) engage in a bidirectional interaction with tumor cells, stem cells, fibroblasts, endothelial cells, B cells, T-cells, and NK cells. In order for a tumor to successfully survive and grow, it both co-opts and suppresses these host responses. Tumors that have large numbers of TAMS are better able to grow.

Many of the TAMS adopt a phenotype referred to as "alternative," also known as M2, as the tumor matures and progresses. This phenotype is in contrast to the highly tumoricidal M1 phenotype. Macrophage phenotype is controlled by cytokines including IL-4 that are produced by infiltrating immune cells and by the tumor cells themselves. The Keegan laboratory studies the signaling mechanisms by which IL-4 and innate sensing of molecular patterns drives the M2 phenotype in vitro and in vivo.

In addition to IL-4, other signals derived from the tumor and the host tissues shape the tumor environment. Hypoxia, lactic acid, and cancer-therapy-induced tissue damage activate innate sensing receptors that help to drive the M2 phenotype. Other factors control the numbers of regulatory T-cells affecting anti-tumor immunity. Ongoing studies analyze whether innate sensing of damaged tumor cells (irradiation or chemotherapy) will enhance M2 differentiation, and in collaboration with **Dr. Svetlana Chapoval**, the mechanism by which Semaphorin 4A increases Treg numbers.

Projects/Grants

VA-Merit 2018-2022
I01BX001850 "Regulation of Macrophage Activation by House Dust Mite"

NIH 2018-2023
RO1AI122631 " Role of Semaphorin 4A in Allergic Inflammation"

NIH 2019-2023
RO1AI143845 "IL-4-activated macrophages: Contribution to allergic lung inflammation linked to viral infection"

Recent Publications

Chapoval, S.P. Hritzo, M., Qi, X., Tamagnone, L., Golding, A. and **Keegan, A.D.** 2019. Semaphorin 4A stabilizes human Treg phenotype via Plexin B1. Immuno Horizons. 3(2) 71-87.

Niharika Khanna, MBBS, MD, DGO

Professor
School of Medicine
Department of Family & Community Medicine
nkhanna@som.umaryland.edu

Recent Publications

Khanna N, Klyushnenkova E. COVID 19 Hotspots And Vulnerable Populations Identified By Area Deprivation Index Mapping 12 May, 2020. Annals of Family Medicine. Pre-print, online COVID collection. Permanent URL: http://hdl.handle.net/2027.42/155341

Khanna N. Complexities in integrating social risk assessment into health care delivery. JABFM 2020 Mar-Apr;33(2):179-181.

Khanna N, Gritzer L, Klyushnenkova E, Montgomery R, Dark M, Shah S, Shaya F. Practice Transformation Analytics Dashboard for Clinician Engagement. Annals of Family Medicine. 2019 Aug 12;17(Suppl 1):S73-S76.

Personal Statement

Niharika Khanna is Professor of Family and Community Medicine at the University of Maryland, School of Medicine (UMSOM) and a member of the Tumor Immunology Program at the Greenebaum Cancer Center, Chief of Population Health at the Department of Family Medicine, Chair of the Maryland Department of Health Cancer Collaborative. In response to the pandemic, Dr Khanna led a population health team to establish a COVID-19 dashboard for the Department of Family Medicine practices to track all screened individuals to ensure seamless communication of results, patient education and management of individuals being tested for SARS CoV2. Funded by the Maryland Department of Health Center for Tobacco Prevention and Control, Dr Khanna has developed an Electronic Health Record clinician decision support solution in Epic electronic health records to electronically connect the Maryland Tobacco Quit Line to reach 154 practices in the University of Maryland Medical System to serve 3,912,403 Maryland residents. Dr Khanna leads the C3I COVID-Smoking initiative to participate in the NCI COVID-Smoking registry to elucidate the association of COVID-19 with tobacco; the registry will include data from 23 participating cancer centers and 170,000 patients. Dr Khanna is a member of the Board of the Maryland Tobacco Quitline and a Member of the CRISP Health Information Exchange Reporting and Analytics Committee. Dr Khanna is the past Director of the Maryland Learning Collaborative for the Garden Practice Transformation Network, funded by the Centers for Medicare and Medicaid Transforming Clinical Practice Initiative(2015-2019), and previously director of the Maryland Health Care Commission's Multi-Payer Program for Patient Centered Medical Homes (MMPP, 2011-2015) to provide clinical implementation of health care reform policies and primary care workforce training in the advanced payment models. Dr. Khanna is a recent NICHD “Building Interdisciplinary Research Careers in Women’s Health (BIRCWH)” scholar (2007-2009). Dr. Khanna’s interests are in clinical translational research to translate research into community programs and specifically in the systems change in primary care. Dr. Khanna is a breast cancer survivor diagnosed in 2009.

Projects/Grants

Center for Tobacco Prevention and Control, Maryland Department of Health grant:

Title: Maryland Tobacco Quitline E-Referral Pilot Project-M0088400678

Goal: To develop a Clinical Decision Support tool to connect electronic health records to the Maryland Tobacco Quitline bidirectionally and enhance practitioner use of this innovation in 154 ambulatory practice clinics at the University of Maryland Medical System.

NCI C3I COVID 19- Smoking Registry administered by the University of Wisconsin subaward

Title: Smoking Status and COVID-19 Complications: The C3I COVID-19 and Smoking Project

Goal: The C3I project seeks to leverage existing relationships between NCI designated Comprehensive Cancer Centers and their associated health systems to collect data on all COVID-positive and COVID-presumptive patients to better understand the relationship between smoking and risk of COVID complications.

Personal Statement

Translational research on pathogenesis of chronic viral infections and translational research to eradicating infections by targeting the virus and the host.

Publications

Shyamasundaran Kottilil, MBBS, PhD

Professor
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Chief, Division of Infectious Diseases
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1. Sherman KE, Abdel-Hameed E, Rouster SD, Shata MT, Blackard JT, Safaie P, Kroner B, Preiss L, Horn L, **Kottilil S**. Improvement in hepatic fibrosis biomarkers associated with CCR5 inactivation through mutation or therapeutic blockade. *Clin Infect Dis* (2018), doi: 10.1093

2. Poonia B, Ayithan N, Nandi M, Masur, H and **Kottilil S** (2018). HBV induces inhibitory FcRL receptor on B cells and dysregulates B cell-T follicular helper cell axis. *Nature Sci Rep* 2018, 8(1):15296

3. Tang L, Covert E, Wilson E, **Kottilil S.** Treatment of Hepatitis B infection: A Systematic Review. *JAMA* 2018 May 1;319(17):1802-1813

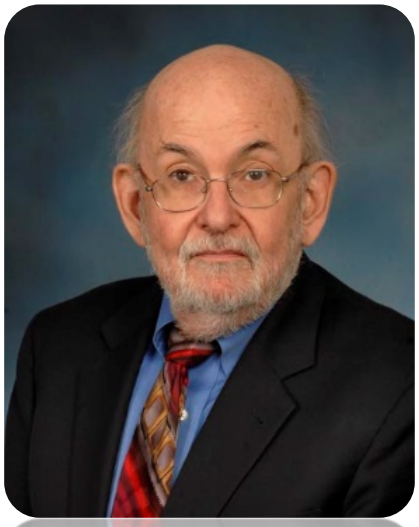
4. Kattakuzhy S, Gross C, Emmanuel B, Teferi G, Jenkins V, Silk R, Akoth E, Thomas A, Ahmed C, Espinosa M, Price A, Rosenthal E, Tang L, Wilson E, Bentzen S, Masur H, **Kottilil** S; and the ASCEND Providers. Expansion of Treatment for Hepatitis C Virus Infection by Task Shifting to Community-Based Nonspecialist Providers: A Nonrandomized Clinical Trial. *Ann Intern Med (*2017) Sep 5;167(5):311-318

5. Kohli, A, Kattakuzhy S., Sidharthan S., Nelson A, McLaughlin M., Seamon C, Wilson E, Meissner EG, Sims Z, Silk R.; Gross C, Tang L, Price A, Jolley TA, Emmanuel B, Proschan M.; Teferi G, Chavez J, Abbott S, Osinusi A, Mo H, Polis MA, Masur H, **Kottilil S**. Four-week Directly Acting Anti-HCV Regimens in HCV Genotype-1 Patients without Cirrhosis: A Phase 2a Cohort Study. *Annals of Intern Med* (2015), 163(12):899-907.

6. Kohli A., Kapoor R, Sims Z, Nelson A, Sidharthan S, Lam B, Silk R, Kotb C, Gross C, Teferi G, Sugarman K, Pang P, Osinusi A, Polis MA, Rustgi V, Masur H and **Kottilil S.** Ledipasvir and Sofosbuvir for Hepatitis C Genotype 4: A Proof of Concept Phase 2a Cohort Study. *Lancet Infect Dis* (2015), Sep;15(9):1049-54.

7. Osinusi A, Townsend K, Kohli A, Nelson A, Seamon C, Meissner EG, Bon D, Silk R, Gross C, Price A, Sajadi M, Sidharthan S, Sims Z, Herrmann E, Hogan J, Teferi G, Talwani R, Proschan M, Jenkins V, Kleiner DE, Wood BJ, Subramanian GM, Pang PS, McHutchison JG, Polis MA, Fauci AS, Masur H, **Kottilil S.** Virologic response to sofosbuvir and ledipasvir in HIV/HCV coinfected patients *JAMA* (2015), 14;314(2):186-7.

8. Osinusi A, Townsend K, Kohli A, Nelson A, Seamon C, Meissner EG, Bon D, Silk R, Gross C, Price A, Sajadi M, Sidharthan S, Sims Z, Herrmann E, Hogan J, Teferi G, Talwani R, Proschan M, Jenkins V, Kleiner DE, Wood BJ, Subramanian GM, Pang PS, McHutchison JG, Polis MA, Fauci AS, Masur H and **Kottilil S.** A Pilot Study to Evaluate the Safety and Efficacy of Ledipasvir/Sofosbuvir in HCV Genotype 1 Subjects Coinfected with HIV Infection. *JAMA* (2015), Mar 24-31;313(12):1232-9.



George K. Lewis, PhD

The Robert C. Gallo, M.D., Professor in Translational Medicine
Director, Division of Vaccine Research, Institute of Human Virology, University of Maryland School of Medicine
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Personal Statement

My principal research interest is the role of antibody specificity and the biophysical chemistry of Fc- mediated effector function. My group provided the first rigorously controlled studies on the relationship between antibody specificity and Fc-mediated effector function. This work has led to new physical chemical insights the mechanisms of Fc-mediated effector function, including antibody-dependent trogocytosis, antibody-dependent cellular cytotoxicity, and antibody-dependent phagocytosis. We have found that antibody binding angles to a single epitope on target cells determines the potency of antibody-dependent cellular cytotoxicity (ADCC) and other Fc-mediated effector functions such as phagocytosis. This work has led to a metric that can predict the Fc-effector function potency based on antigen-antibody structural data. Additionally, we recently published the most definitive data to date of an antigen-induced allosteric communication network between the Fab and Fc regions of human IgG1 that control the binding to low-affinity FcgR. This network also includes residues at the CH2-CH3 interface of Fc that interact with a wide variety of ligands including TRIM-21, DCSIGN, Rheumatoid Factors, Protein A, and Protein G.

Projects/Grants

NIAID, NIH Structural Targeting of Potentially Protective gp120 Epitopes in the C1/C2 Region 5R01AI116274

NIAID, NIH Durable Antibody Mediated Protection Against HIV 5P01AI124912

NIAID, NIH Bridging Antibody Fc-Mediated Antiviral Functions Across Humans and Nonhuman Primates 5P01AI120756

Recent Publications

Orlandi C, Deredge D, Ray K, Gohain N, Tolbert W, DeVico AL, Wintrode P, Pazgier M, **Lewis GK**. 2020. Antigen-Induced Allosteric Changes in a Human IgG1 Fc Increase Low-Affinity Fcgamma Receptor Binding. Structure doi:10.1016/j.str.2020.03.001.

Gilchuk P, Murin CD, Milligan JC, Cross RW, Mire CE, Ilinykh PA, Huang K, Kuzmina N, Altman PX, Hui S, Gunn BM, Bryan AL, Davidson E, Doranz BJ, Turner HL, Alkutkar T, Flinko R, Orlandi C, Carnahan R, Nargi R, Bombardi RG, Vodzak ME, Li S, Okoli A, Ibeawuchi M, Ohiaeri B, **Lewis GK,** Alter G, Bukreyev A, Saphire EO, Geisbert TW, Ward AB, Crowe JE, Jr. 2020. Analysis of a Therapeutic Antibody Cocktail Reveals Determinants for Cooperative and Broad Ebolavirus Neutralization. Immunity 52:388-403 e12.

Lewis GK, Ackerman ME, Scarlatti G, Moog C, Robert-Guroff M, Kent SJ, Overbaugh J, Reeves RK, Ferrari G, Thyagarajan B. 2019. Knowns and Unknowns of Assaying Antibody-Dependent Cell-Mediated Cytotoxicity Against HIV-1. Front Immunol 10:1025.

Yang Liu, PhD

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Personal Statement

My laboratory studies the fundamental mechanism of immune recognition and cancer biology. We have been at the forefront in studying the biology of CTLA-4 and immunotherapy. We are among the first group to identify CTLA4 ligand distinct from CD80 (which is now called CD86 or B7-2) (A1). We are also among the first to generate anti-human CTLA-4 mAb and independently demonstrate that these antibodies confer resistance to cancer cells in various humanized mouse models (A2, A3). Our work leads to a new concept that cancer immunity and autoimmunity induced by anti-CTLA-4 mAb are not necessarily linked (A3, A4). Our recent studies focus on both fundamental mechanism that uncovers the link between autoimmunity and cancer immunity and on translating this new concept for production of new generation of anti-CTLA-4 mAb.

Projects/ Grants

R01 AI064350 (Y. Liu, P. Zheng) 01/01/2005 – 01/31/2021
NIH/NIAID Checkpoint for Host Response to Tissue Injuries
The goal of this study is to investigate negative regulation of host response to danger-associated molecular pattern in non-septic tissue injury.
Role: PI

R01 FD006089-01 (Liu) 09/01/2018 – 08/30/2022
Phase 2b Study of CD24Fc for the Prevention of Graft versus Host Disease..
This grant support a multi-center randomized, double blind, placebo controlled Phase IIb study of CD24Fc for the prevention of graft versus host disease (GVHD) in 180 patients.
Role: PI

R01 1R01AI154722 (Liu) 08/07/2020 – 07/31/2025
PRESERVING CTLA-4 IMMUNE CHECKPOINT FOR SAFER AND MORE EFFECTIVE CANCER IMMUNOTHERAPY
This grant aims to establish a fundamental mechanism and treatment for Immunotherapy related adverse events associated with anti-PD-1 and anti-CTLA-4 combination therapy.
Role: PI

Recent Publications

1.Xuexiang Du, Mingyue Liu, Juanjuan Su, Rhonda Flores, Fei Tang, Peiying Ye, Martin Devenport, Xu Wang, Yan Zhang, **Yang Liu** and Pan Zheng. Uncoupling Therapeutic from Immunotherapy-related Adverse Effects for Safer and Effective Anti-CTLA-4 Antibodies in CTLA4 Humanized Mice. *Cell Res*. 2018 Feb 20. doi: 10.1038/s41422-018-0012-z. [Epub ahead of print] PMID: 29463898

2. Zhang Y, Du X, Liu M, Tang F, Zhang P, Ai C, Fields JK, Sundberg EJ, Latinovic OS, Devenport M, Zheng P, **Liu Y.** Hijacking antibody-induced CTLA-4 lysosomal degradation for safer and more effective cancer immunotherapy. Cell Res. 2019 Jul 2. doi: 10.1038/s41422-019-0184-1

Tim Luetkens, MD

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Personal Statement

The goal of Dr. Luetkens' research is the translational development of novel immunotherapies for the treatment of cancer. In particular, he is focusing on developing safe and effective receptor-transgenic T cells targeting antigens specifically expressed by tumor cells. He has developed high-throughput platforms for the development and screening of novel chimeric antigen receptors and monoclonal antibodies and is working on novel protein engineering approaches to facilitate the wider use of cellular immunotherapies in pediatric cancers.

Projects/Grants

Efficacy and toxicity of IFNG-synNotch T cells for the treatment of neuroblastoma.

A genetic approach to prevent CAR T cell mediated neurotoxicity.

Recent Publications

CD229 CAR T cells eliminate multiple myeloma and tumor propagating cells without fratricide. Radhakrishnan SV, **Luetkens T**, Scherer SD, Davis P, Vander Mause ER, Olson ML, Yousef S, Panse J, Abdiche Y, Li KD, Miles RR, Matsui W, Welm AL, Atanackovic D. Nat Commun. 2020 Feb 7;11(1):798.

In vivo vaccination effect in multiple myeloma patients treated with the monoclonal antibody isatuximab. Atanackovic D, Yousef S, Shorter C, Tantravahi SK, Steinbach M, Iglesias F, Sborov D, Radhakrishnan SV, Chiron M, Miles R, Salama M, Kröger N, **Luetkens T.** Leukemia. 2020 Jan;34(1):317-321.

Dean L. Mann, MD
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Personal Statement

We have completed laboratory studies (CMC) required by the FDA for submission of an application to treat advanced cancer patients with a combination immunotherapy and standard of care radiation.

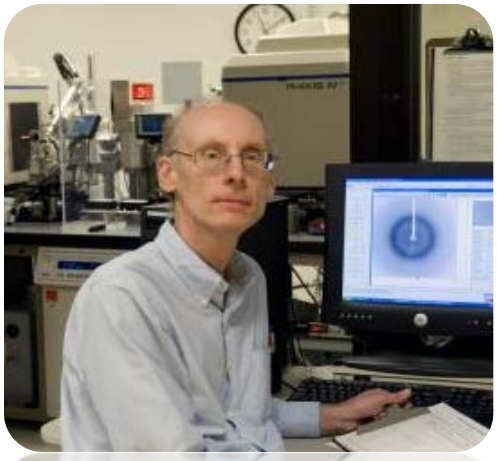
Projects/Grants

Grant from the Hasumi International Research Foundation
Development of a Dendritic Based Vaccine for Treatment of Advanced Cancer

Cooperative Agreement: National Cancer Institute /University of Maryland
Case control study of cancer in the State of Maryland

Recent Publications

Co-author : A Viral Exposure Signature Defines Early Onset of Hepatocellular Carcinoma
Cell 182 317-328 2020



Roy Mariuzza, PhD

Professor
Department of Cell Biology and Molecular Genetics,
Institute for Bioscience & Biotechnology Research,
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Personal Statement

Research in Dr. Roy Mariuzza's laboratory focuses on understanding how immune system cell surface receptors recognize molecules. Several classes of recognition molecules are under study: antibodies, T cell receptors (TCRs), natural killer (NK) cell receptors, and variable lymphocyte receptors (VLRs).

Projects/Grants

R01 AI144422
(Vignali, Mariuzza, Workman)
01/08/2019-12/31/2023
Structure, Function and Mechanistic Analysis of LAG3
The major goals of this project are to determine the structure and mechanism of action of the T cell inhibitory receptor LAG3.

Recent Publications

Wu D, Gallagher DT, Gowthaman R, Pierce BG, Mariuzza RA. (2020) **Structural basis for oligoclonal T cell recognition of a shared p53 cancer neoantigen.** Nature Communications 11(1):2908.

Mishra, A. K., and R. A. Mariuzza. 2018. "Insights into the structural basis of antibody affinity maturation from next-generation sequencing. *Front Immunol* 9:117.

Li, S. Shun et al. 2018. "Identification of the fungal ligand triggering cytotoxic PRR-mediated NK cell killing of Cryptococcus and Candida. *Nat Commun* 9:751.

Rangarajan, S. et al. 2018. Peptide-MHC (pMHC) binding to a human antiviral T cell receptor induces long-range allosteric communication between pMHC- and CD3-binding sites. *J Biol Chem* 293:15991.

Ryan M. Pearson, PhD

Assistant Professor
School of Pharmacy, Department of Pharmaceutical Sciences
School of Medicine, Department of Immunology
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Personal Statement

Research in the Pearson laboratory (www.RyanPearsonLab.com) aims to develop biomaterial-focused strategies to treat dysregulated immune responses associated with severe inflammation and sepsis, autoimmunity and allergy, and cancer through the intersection of two enabling disciplines, nanotechnology and immune engineering. Three major research themes guide our group: (i) elucidating the inherent immunomodulatory properties of biomaterials; (ii) investigating the genetic and non-genetic reprogramming events induced by biomaterials on innate and adaptive immune cells, and (iii) engineering nanobio interactions through controlled biomaterial synthesis and nanoparticle formulation for targeted drug delivery *in vivo*. Our lab has significant expertise in nanoparticle-based drug and gene delivery for immunomodulation, bioconjugation, polymer synthesis, and animal models of EAE, endotoxemia, allergic airway hypersensitization, and heterotopic ossification.

Projects/Grants

New Investigator Award (American Association of Colleges of Pharmacy); "Programming immune cell sensitivity towards Toll-like receptor activation"
Innovative Collaboration Pilot Grant (UMB Institute for Clinical and Translational Science (1UL1TR003098); "Engineering B cell modulating vaccines for T cell cancer immunotherapy"
Maryland Industrial Partnerships Phase I *(Mtech)*; "CFZ Delivery to Colon with EK101 for CDI Treatment"
Maryland Industrial Partnerships Phase II *(Mtech)*; "Formulation Development for Bone Control Therapy"

Recent Publications

1. Chakraborty, A., Lasola, J.J.M., Truong, N., Pearson, R. M., Serum-independent non-viral gene delivery to innate and adaptive immune cells using immunoplexes. ***ACS Applied Bio Materials*** 2020. doi.org/10.1021/acsabm.0c00761. In press.

2. Lasola, J.J.M., Kamdem, H., McDaniel, M., Pearson, R. M., Biomaterial-driven immunomodulation: Cell biology-based strategies to mitigate severe inflammation and sepsis. ***Frontiers in Immunology*** 2020. doi.org/10.3389/fimmu.2020.01726.

3. Casey, L.M., Kakade, S., Decker, J.T., Rose, J., Deans, K., Shea, L.D., Pearson, R. M. Cargo-less nanoparticles program innate immune cell responses to Toll-like receptor activation. ***Biomaterials*** 2019, 218, 119333.

Darren Perkins, PhD

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Personal Statement

My research program is focused on how inflammatory responses are triggered by sensors of cellular damage or infection that operate as components of the innate arm of the human immune system. In particular, I am interested in how these sensors trigger production of type I interferons (IFN), important cytokines that amplify immune responses against tumors or pathogenic microbes. I am also very interested in the rapidly emerging field of immune modulating small lipids, called eicosanoids, and how these eicosanoids can function as powerful antagonists of interferon responses.

Projects/Grants

PGE2 RECEPTOR SUPPRESSION OF CGAS/STING RESPONSES IN ANTI-TUMOR IMMUNITY.
Funded by grant 1R21AI152051-01
The strength of the inflammatory signature in the tumor microenvironment (TME) is a critical determinant of the host anti-tumor immune response. Type I Interferon (IFN) production by tumor tissue directly or by tumor associated macrophages and dendritic cells can increase the inflammatory potential of the TME and significantly increase spontaneous cell mediated anti-tumor responses (e.g. CD8 T and NK). The cGAS/STING innate immune sensor system has recently been uncovered as a major driver of IFN production in the TME and this has generated considerable interest in pharmacologic stimulation of cGAS/STING alone and in conjunction with other immuno-therapies. However, how tumors may evade or minimize cGAS/STING responses in response to agonists is an open question. We have found that activators of the cGAS/STING axis trigger a coincident prostaglandin PGE2 response which potently suppresses STING dependent IFN production through specific PGE2 receptors. This PGE2 autocrine negative feedback loop likely functions to limit the extent of cGAS/STING IFN production both from the tumor tissue itself, and from tumor associated innate immune cells. The overall goal of this project is to understand the mechanism of PGE2 production during cGAS/STING responses in tumors, and to determine whether inhibition of one PGE2 receptor, can contribute to tumor control in in vivo pre clinical models.

Recent Publications

1) Katharina Richard, Stefanie N Vogel, **Darren J Perkins**. “Quantitation of TLR4 internalization in response to LPS in thioglycollate elicited peritoneal mouse macrophages by flow cytometry”. Bio Protoc. 2019 Sep 20;9(18):e3369.

2) Katharina Richard, **Darren J. Perkins**, Erin Harberts, Song Y, Archana Golapakrishnan, Kari Ann Shirey, Wendy Lai, Alexandra Vlk, Anup Mahurkar, Lynn Hawkins, Robert K. Ernst, Stefanie N. Vogel. “Dissociation of TRIF bias and Adjuventicity”. Vaccine. 2020 Jun 2;38(27):4298-4308.

Brian Pierce, PhD

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Personal Statement

My research is focused on modeling and design of immune recognition using advanced computational structural biology tools. This includes modeling T cell receptors from sequence and designing their affinities using structure-based design, computational docking to predict antibody-antigen complex structures, and structure-based optimization of antibodies to improve targeting. We work collaboratively with experimental laboratories to model, design, and characterize TCRs and antibodies of interest.

Projects/Grants

“High resolution modeling and design of T cell receptors” (NIH R01 grant)

“Design of immunologically intact soluble HCV E1E2 complexes using transmembrane-mimic scaffolds” (NIH R21 grant)

Recent Publications

Wu D, Gallagher DT, Gowthaman R, Pierce BG, Mariuzza RA. (2020) **Structural basis for oligoclonal T cell recognition of a shared p53 cancer neoantigen.** Nature Communications 11(1):2908.

Daniels J, Doukas PG, Martinez Escala, ME, Ringbloom KG, Shih DJH, Yang J, Tegtmeyer K, Park J, Thomas JJ, Selli ME, Altunbulakli C, Gowthaman R, Mo SH, Balaji J, Pease DR, Pro B, Abdulla FR, Shea C, Sahni N, Gru AA, Pierce BG, Louissaint Jr A, Guitart J, Choi J. (2020) **Cellular origins and genetic landscape of cutaneous gamma delta T cell lymphomas.** Nature Communications 11, 1806.

Gowthaman R, Pierce BG. (2020) **Modeling and viewing T cell receptors using TCRmodel and TCR3d.** Bioinformatics for Cancer Immunotherapy. Methods in Molecular Biology 2120:197-212

Aaron P. Rapoport, MD

Gary Jobson Professor of Medical Oncology
Director, Blood and Marrow Transplant Program, UM Marlene and Stewart Greenebaum Comprehensive Cancer Center
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Projects/Grants

2 P30 CA134274-09
08/04/16-07/31/21

Tumor Immunology and Immunotherapy (TII) at UMGCC
The goal of the TII Program is to develop and implement immune-based strategies to prevent, treat, and/or monitor malignant diseases and disease progression.

Personal Statement

Dr. Rapoport is a board-certified hematologist and stem cell transplant physician with more than 25 years of experience in the care of patients with hematopoietic neoplasms and benign hematologic disorders. He has conducted translational research focused on the use of costimulated autologous T cells and vaccines to enhance immune recovery after autologous stem cell transplants for hematologic malignancies. He has directed major clinical trials of adoptive T-cell therapy. These clinical trials have provided a new avenue for rapid reconstitution of T-cell–mediated immunity following blood/marrow transplantation and laid the groundwork for the development of effective cellular immunotherapy of myeloma.

Recent Publications

Long-term safety and activity of NY-ESO-1 SPEAR T cells after autologous stem cell transplant for myeloma.
Stadtmauer EA, Faitg TH, Lowther DE, Badros AZ, Chagin K, Dengel K, Iyengar M, Melchiori L, Navenot JM, Norry E, Trivedi T, Wang R, Binder GK, Amado R, **Rapoport AP**. Blood Adv. 2019 Jul 9;3(13):2022-2034. doi: 10.1182/bloodadvances.2019000194. PMID: 31289029

Characteristics and outcomes of therapy-related myeloid neoplasms after treatment for multiple myeloma.
Duong VH, Holtzman NG, Koka R, Singh ZN, Zou Y, Emadi A, **Rapoport AP**, Kocoglu MH, Baer MR, Badros AZ. Leuk Lymphoma. 2019 Jul 8:1-4. doi: 10.1080/10428194.2019.1633639. [Epub ahead of print] No abstract available. PMID: 31282234

Radiation Therapy as a Bridging Strategy for CAR T Cell Therapy With Axicabtagene Ciloleucel in Diffuse Large B-Cell Lymphoma.
Sim AJ, Jain MD, Figura NB, Chavez JC, Shah BD, Khimani F, Lazaryan A, Krivenko G, Davila ML, Liu HD, Falchook AD, Dahiya S, **Rapoport AP**, Kim S, Locke FL, Robinson TJ. Int J Radiat Oncol Biol Phys. 2019 Jun 5. pii: S0360-3016(19)30819-3. doi: 10.1016/j.ijrobp.2019.05.065. [Epub ahead of print] PMID: 31175906

Long-term remissions after stopping pembrolizumab for relapsed or refractory multiple myeloma.
Badros AZ, Ma N, **Rapoport AP**, Lederer E, Lesokhin AM.
Blood Adv. 2019 Jun 11;3(11):1658-1660. doi: 10.1182/bloodadvances.2019000191. No abstract available. PMID: 31167817

Refractory postallogeneic stem cell transplant pure red cell aplasia in remission after treatment with daratumumab.
Bathini S, Holtzman NG, Koka R, Singh Z, Wilding E, Zou Y, Ruehle K, Kocoglu MH, Badros A, Hardy N, Yared J, **Rapoport AP**, Fontaine M, Emadi A, El Chaer F, Dahiya S.Am J Hematol. 2019 Aug;94(8):E216-E219.
doi: 10.1002/ajh.25515. Epub 2019 Jun 7.
No abstract available.
PMID: 31120638

Katherine L. Seley-Radtke, PhD

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Personal Statement

Medicinal/Synthetic Bioorganic/Organic Chemistry and Drug Design: Discovery, design and synthesis of nucleoside/nucleotide and heterocyclic enzyme inhibitors with chemotherapeutic emphasis in the areas of antiviral, anticancer, antibiotic, and antiparasitic targets. Primary goals include development of potent inhibitors to shut down disease replication pathways through a combination of cross-disciplinary synthetic, biological screening, mechanistic, and structure-based drug design techniques.

Projects/Grants

The primary focus for the Seley-Radtke laboratories involves the design and synthesis of flexible nucleoside ("fleximers") and nucleobases ("flex-bases) inhibitors as a powerful approach to overcome the development of drug resistance. The fleximers are able retain full potency when faced with "escape mutations" in biologically critical enzymatic systems - the inherent flexibility of the inhibitors allows them to conformationally adjust to point mutations encountered in the binding site, and to engage secondary amino acids not previously involved in the enzyme's mechanism of action. Potent activity has been uncovered with a series of "doubly flexible" acyclic nucleosides and their corresponding prodrugs against various viruses including coronaviruses such as SARS, MERS and now SARS-CoV-2, as well Ebola, Marburg, Tickborne Encephalitis, Zika, Dengue and Yellow Fever, among other high priority neglected diseases. To date, low micromolar to nanomolar levels of activity have been observed and several are currently in preclinical animal studies. In addition to viral targets, another project focuses on the use of nucleobases as anticancer agents. Following upon the recent observation that several nucleobase analogues have exhibited selective and highly potent (sub-nanomolar) levels of activity against several key cancers including lung, colon, leukaemia, renal, and triple negative breast cancers (among others), we have initiated a program to elucidate their mechanism of action, as well as to further study their highly promising activity in vitro and in vivo. These compounds have advanced to animal studies and as well as investigations to elucidate their mechanism of action.

Recent Publications

Thames, J. E.; Waters III, C. D.; Valle, C.; Bassetto, M.; Aouadi, W.; Martin, B.; Falat, A.; Coutard, B.; Brancale, A.; Canard, B.; Decroly, E.; *Seley-Radtke, K. L. "Synthesis and Biological Evaluation of Novel Flexible Nucleoside Analogues that Inhibit Flavivirus Replication In Vitro" *Bioorg Med Chem* **in press.**

Vichier-Guerre, S.; Ku, T.; Pochet, S.; Seley-Radtke, K. L.* "An expedient synthesis of flexible nucleosides through enzymatic glycosylation of proximal and distal fleximer bases", *ChemMedChem*, **2020,** *21*, 1412-1417 **(featured article and cover).**

Cawrse, B. M.; Robinson, N. M.; Lee, N. C.; Wilson, G. M.; *Seley-Radtke, K L.; Structural and biological Investigations for a series of N-5 substituted pyrrolo[3,2-*d*]pyrimidines as potential anticancer therapeutics. *Molecules: Bioactive Nucleosides and Nucleotides* **2019**, *24*, 2656-68; doi:10.3390/molecules24142656.

Nevil J Singh, PhD

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Recent Publications

Matson CA, Choi S, Livak F, Zhao B, Mitra A, Love PE, **Singh NJ**. CD5 dynamically calibrates basal NF-κB signaling in T cells during thymic development and peripheral activation. *Proc Natl Acad Sci U S A*. 2020 Jun 23;117(25):14342-14353. doi: 10.1073/pnas.1922525117.

Grossman Z, **Singh NJ**, Simonetti FR, Lederman MM, Douek DC, Deeks SG. 'Rinse and Replace': Boosting T Cell Turnover To Reduce HIV-1 Reservoirs. *Trends Immunol.* 2020 Jun;41(6):466-480

Matson CA, **Singh NJ**. Manipulating the TCR signaling network for cellular immunotherapy: Challenges & opportunities. *Mol Immunol.* 2020 Jul;123:64-73. doi: 10.1016/j.molimm.2020.04.007

Personal Statement

Our lab is interested in understanding the fundamental mechanisms regulating T cell activation. Over the years we have used mouse model systems to dissect the cellular and molecular processes governing dendritic cell activation, T cell responses and protective immunity in vivo. Our studies have identified new roles for the IL-12p40 cytokines made by dendritic cells on T cell responses, influence of neural factors on T cell activation, cell intrinsic tuning of T cells during acute vs chronic stimulation etc. The significance of these studies is also that they pinpoint new and out-of-the-box targets for developing strategies for immunotherapy to a variety of threats, including tumors.

Projects/Grants

The most recent projects in our lab relevant to tumor immunotherapy are:

1. Neural factors are known to regulate various aspects of immune function. We recently found that the Vasoactive Intestinal Peptide (VIP) acts on naïve T cells, even before antigen activation to drive enhanced TH17/Th22 differentiation. Further, preliminary studies indicate that VIP directly modulates the ability of the T cell receptor to signal after engaging antigen. This suggests that the milieu a T cell occupies even before it encounters a tumor antigen could significantly alter the long term consequences of a tumor-specific T cell response.

2. Examining signaling properties of peripheral T cells, we found that each T cell can maintain different levels of the critical signaling molecule NFkB. Intriguingly, using conditional knockouts and single cell imaging assays, we find that the cell surface molecule CD5 precisely calibrates a cell's NFkB depot. This offers new avenues for improving adoptive immunotherapy by selecting on or manipulating CD5 levels on T cells.

3. The balance between IFNg and IL4/IL10 is a critical indicator of successful effector immunity against tumors. The cytokine IL-12 is a potent inducer of IFNg and essential for tipping this balance towards robust anti-tumor immunity. Our recent studies have identified a new member of this family of cytokines, which seems to have an opposing effect, directing T cells towards an IL4/IL10 producing phenotype. We have developed specific mAbs to block this, which may be helpful in pushing intratumoral phenotypes away from a tumor-promoting one.

Nicholas M. Stamatos, MD, PhD

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Personal Statement

Dr. Stamatos' academic career combines the challenges and rewards of practicing clinical medicine and conducting basic research. He attends on the HIV/Medicine inpatient service and on the Infectious Diseases Cancer Center/Bone Marrow Transplant and Medical Intensive Care Unit consult services, as well as at an outpatient Infectious Diseases clinic. He plays an integral role in training Infectious Disease fellows, postdoctoral research fellows, medical housestaff and students in both the clinic and the laboratory. With a special interest in virology and glycoimmunology, he also conducts research that is focused on understanding how modulation of the carbohydrate content of cell surface glycoproteins and glycolipids influences the functional capacity of peripheral blood mononuclear cells, including their interaction with HIV-1. His laboratory has shown that desialylation of glycoconjugates on the surface of purified human monocytes activates cells, stimulates production of cytokines (e.g. IL-12p40, TNFa, and IL-6), and enhances the responsiveness of monocytes to lipopolysaccharide (LPS). His work suggests that inhibition of endogenous sialidases may be a therapeutic target during LPS-mediated infections. His work also pioneered the growing appreciation that Neu1 sialidase, previously deemed to be strictly a lysosomal protein, is present and active on the cell surface. His laboratory was first to show the importance of polysialic acid (polySia) in the immune system by demonstrating that neuropilin-2 (NRP-2) is expressed on the surface of human dendritic cells (DC) and is polysialylated. His laboratory's discovery of polysialylated NRP-2 on DC has engendered numerous studies from other laboratories that demonstrate a direct role of polySia in DC migration and has generated great interest in identifying additional polysialylated cells in the immune system. Although much is known about the glycosylation of HIV-1 envelop proteins, relatively little is known about how glycosylation of proteins on the surface of permissive lymphocytes affects infection. He previously demonstrated that removal of sialic acid from the surface of peripheral blood mononuclear cells using an exogenous bacterial neuraminidase promoted infection with HIV-1. In contrast to work on monomeric sialic acid, he has also found that removal of polySia from a specific protein on the surface of lymphocytes or in the extracellular milieu markedly inhibits infection. The results from his studies are expected to identify a novel target for treatment of HIV infection and provide a blueprint for down-regulating the expression of polySia or modified protein(s) in activated lymphocytes, as well as in other cells susceptible to infection with HIV-1. The overarching goal of research in his laboratory is to demonstrate that sialic acid, sialidases and sialyltransferases are potential targets for therapeutic agents during infectious and inflammatory conditions.

Recent Publications

Curreli, S., Wong, B.S., Latinovic, O., Konstantopoulos, K. and **Stamatos, N.M.** 2016. Class 3 semaphorins induce F-actin reorganization in human dendritic cells: role in cell migration *J. Leukoc. Biol*. Dec;100(6):1323-1334. PMID: 27406993

Marcelo B. Sztein, MD

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Recent Publications

Edelman, R., Deming, M.E., Toapanta, F.R., Heuser, M.D., Chrisley, L., Barnes, R.S., Wasserman, S.S., Blackwelder, W.C., Handwerger, B.S., Pasetti, M., Siddiqui, K.M., **Sztein, M.B**. The SENIEUR protocol and the Efficacy of Hepatitis B Vaccination in Healthy Elderly Persons by Age, Gender, and Vaccine Route. Immunity and Ageing. 17:9, 2020. PMID: 32355503. PMC7187507.

Booth, J.S., Goldberg, E., Barnes, R.S., Greenwald, B.D., **Sztein, M.B.** Resident memory CD4+ T cells elicited in the human terminal ileum lamina propria and epithelial compartments by oral typhoid vaccination. J. Translational Medicine. 18: 102, 2020. PMID: 32098623. PMC7043047

Personal Statement

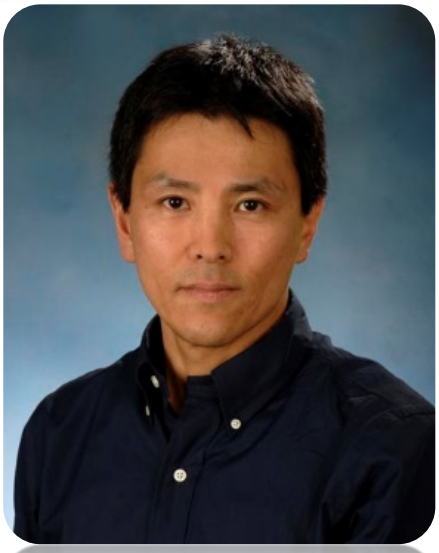
My research experience over the past 35 years focused on the regulatory mechanisms of innate and acquired immunity in response to infection in animal models and on translational studies in humans (both in the US and internationally in developing and developed countries) with the overarching goal of applying this knowledge to accelerate the development of new and more effective vaccines. To date, I have authored or co-authored 232 manuscripts in peer-reviewed journals and 33 invited chapters in the fields of immunology, vaccines and infectious diseases In 2002 I established the Immunology Group at the Center for Vaccine Development (CVD-IG), UMSOM to centralize and expand interdisciplinary efforts in translational research with the ultimate goal of accelerating vaccine development. Models of infectious diseases encompass the study of systemic and gastrointestinal mucosal immune responses in subjects participating in challenge studies with wild-type organisms and/or in vaccine trials of genetically engineered vaccine strains such as attenuated *S.* Typhi and *Shigella* (alone or as a carrier of foreign genes), V. cholera, Enteroaggregative *E. coli*, ETEC, *Plasmodium falciparum*, *S.* Paratyphi A, *S.* Paratyphi B, non-typhoidal *Salmonella* (NTS), and invasive NTS, as well as Dengue virus, *Francisella tularensis*, influenza, hepatitis and Ebola. I have been continuously funded by NIH since 1986. Over the past 25 years I have directly mentored and supervised more than 25 postdoctoral fellows, medical fellows, graduate students and visiting scientists. I have extensive experience in managing large multidisciplinary teams of investigators as part of NIH contracts and U19 grants. I am an expert in flow cytometry, having been involved in this field since 1984 and directing flow cytometry core facilities for almost 30 years. About 7 years ago, I was among the first investigators to make use of the sate-of-the-art mass cytometer technology which allows the measurement of 45+ parameters/cell. At present my facility has 2 Helios mass cytometers, a 6-way sorter and other analytical flow cytometers which has been used for cancer-related projects. I serve as Co-Director of the Flow Cytometry Shared Service.

Projects/Grants

NIH Grant. R01-AI036525. Immune mechanisms of protection in S. Typhi infection and vaccination in humans. Marcelo B. Sztein, P.I. 06/12/2019 - 05/31/2024. $2,835,215 total costs (all years).

NIH Grant. U19-AI142725. Active Vaccination and Passive Antibody Strategies to Prevent Disease Caused by Multidrug-Resistant Bacterial Pathogens. Myron M. Levine, U19 PI. Marcelo B. Sztein, PL of Research Project 5 titled “Defining immunological mechanisms of serovar cross-reactivity to develop broad spectrum protective vaccines for typhoidal and non-typhoidal Salmonella infections in humans”. Research Project 5 total costs $2,850,506 (all years). 03/15/2019 - 02/29/2024.

NIH. T32AI007524. Fellowship Training Program in Vaccinology. Kathleen Neuzil and Marcelo B. Sztein, Multi-PIs. Overall T32 Co-Director, Director of the Pathogenesis, Immunology and Antigen Discovery Track, and Permanent member of the Advisory Committee. 07/01/2018 – 06/30/2023. $1,594,640 direct costs (all years).



Yutaka Tagaya, MD, PhD

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Recent Publications

IL-2 and IL-15 blockade by BNZ-1, an inhibitor of selective γ-chain cytokines, decreases leukemic T-cell viability.Wang TT, Yang J, Zhang Y, Zhang M, Dubois S, Conlon KC, Tagaya Y, Hamele CE, Dighe S, Olson TL, Feith DJ, Azimi N, Waldmann TA, Loughran TP Jr.Leukemia. 2019:1243-1255. doi: 10.1038/s41375-018-0290-y. PMID: 30353031

Results From a First-in-Human Study of BNZ-1, a Selective Multicytokine Inhibitor Targeting Members of the Common Gamma (γc) Family of Cytokines. Frohna PA, Ratnayake A, Doerr N, Basheer A, Al-Mawsawi LQ, Kim WJ, Zapata JC, Wu X, Waldmann TA, Azimi N, Tagaya Y.J Clin Pharmacol. 2020;60(2):264-273. doi: 10.1002/jcph.1522. PMID: 31465127

Personal Statement

My research interest is on the mechanistic understanding of the cellular activation of lymphocytes. This includes oncogenic transformation. I approach cancer biology from two independent paths. One is how retrovirus (human T-cell leukemia virus-1, HTLV-1) transforms CD4 T-cells. My lab also develops a novel immunotherapy on this viral leukemia (called adult T-cell leukemia0 because there exists no effective therapy and ATL is fatal. In addition, I am interested in the role of gc (common-gamma) family cytokines in normal and pathologic T-cell activation. We developed a novel concept of co-inhibiting multiple cytokines that belong to a family (and hence share structure, receptor and function). We have generated a few multi-cytokine inhibitors based on this idea (which is the first demonstration of the proof of this concept). These inhibitors inhibit more than 2 cytokines from the gc-family (including IL-2. -4, -7, -9, -15, and -21) and we demonstrated the critical need to suppress functionally redundant cytokines to control pathogenic activation of lymphoid in human hematopoietic malignancies. Currently we are conducting a phase II clinical trial targeting human T-cell malignancies using our new inhibitors.

Projects/ Grants

The phase I/II clinical trial using our IL-2/IL-15 co-inhibiting peptide aims at treating two human T-cell malignancies (Large-Granular Lymphocyte Leukemia, LGLL and cutaneous T-cell lymphoma (CTCL) that are currently without cure (NCT 03239392). We are treating cases that were refractory to conventional and investigational treatments. Patients were grouped into cohorts with different dosing of the PEGylated inhibitor and received weekly injections for 3 months. With LGLL, we saw specific apoptotic response of leukemic cells during the treatment, and consequently leukemic cells decreased in number in response to the treatment. We also observed the improvements of other clinical symptoms associated with LGLL, such as severe anemia and neutropenia in response to the treatment. This is a first-in-human proof that leukemic cells in LGLL depends on IL-15 and/or IL-2 (which we have demonstrated in an ex vivo study) and that intervention to this mechanism is therapeutically efficacious. The overall response rate (ORR) was around 30% with minimum adverse effects. With CTCL, again around 40% of the patients showed improvements of skin legions. Curiously, we have preliminary data that our treatment targets inflammatory CD8 T-cells that strongly express Perforin and Granzyme B and the improvements of clinical scores (mSWAT) correlate well with the disappearance inflammatory CD8 T-cells, thus providing potentially new mechanism of action in decreasing the disease burden of CTCL. Collectively, our IL-2/IL-15 co-inhibition strategy provides a novel and safe strategy in treating LGLL and CTCL. Notably, prognosis of these malignancies is poor once the disease entered the aggressive phase, though the disease slowly progress. Since the mechanism of action of our treatment might be complementary to other existing anti-LGLL/CTCL treatments, we are also investigating the possibility of combining IL-2/IL-15 co-inhibition with other existing treatments for better efficacy.

Stefanie N. Vogel, PhD

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Grants

NIH R01 AI123371 (PI: Vogel)

R01 AI125215 (MPI: Vogel/Blanco)

R01 AI143845 (MPI: Keegan/Vogel/Viscardi)

T32 AI095190 (PD: Vogel)

S10 OD025101 (PI: Vogel)

Personal Statement

For ~40 years, my work has focused on the analysis of the fundamental mechanisms by which macrophage differentiation facilitates or restricts infectious agents or tumor growth. My laboratory has made seminal contributions to the area of immunology that we now call "innate immunity," and specifically, the mechanisms by which Toll-like receptor (TLR) signaling is regulated. We have characterized many of the fundamental mechanisms by which TLR agonists, such as Gram negative lipopolysaccharide (LPS), and cytokines and interferons, regulate macrophage functions. The creative use of genetic, molecular, and biochemical approaches, combined with unique animal models of infection, has led to our most recent, highly translational work, resulting in novel therapeutic approaches for influenza and respiratory syncytial virus (RSV), development of small molecule TLR antagonists based on the structural interactions of innate signaling molecules, and a prototype vaccine for the biothreat agent, *Francisella tularensis*. I have published ~300 peer-reviewed publications plus ~50 invited works, have mentored 39 post-doctoral fellows and 15 graduate students, and currently direct of a T32 entitled "Signaling pathways in innate immunity." I have had continuous NIH funding for more than 38 years, as well as other sources of grant support.

Projects

We have identified a novel host-derived mediator that contributes to influenza-induced disease, Gastrin Releasing Peptide (GRP). Together with other host-derived "danger associated molecular patterns," *e.g.*, HMGB1, and the pattern recognition receptor, TLR4, we have made significant translational strides to treat this disease.

We have shown prostaglandin E_2 to be an important negative feedback inhibitor of TLR4-mediated interferon production. This is the first negative regulator identified for this signaling pathway.

Recent Publication

K. A. Shirey, W. Lai, L. J. Brown, J. C. G. Blanco, Y. Wang, R. Beadenkopf, **S. N. Vogel**, G. A. Snyder. Select targeting of intracellular Toll-Interleukin-1 Receptor Resistance domains for protection against influenza-induced disease. *Innate Immun.* 26: 26-34 (2020). PMC6974880.

K. Richard, D. J. Perkins, K. E. M. Harberts, Y. Song, A. Gopalakrishnan, K.A. Shirey, W. Asi, A. Vlk, A. Mahukar, S. Nallar, L. D. Hawkins, R. K. Ernst, **S. N. Vogel**. Dissociation of TRIF bias and adjuvanticity. *Vaccine* (2020) 38: 4298-4308. PMC7302928

D. J. Prantner, S. Nallar, K. Richard, D. Spiegel, K. D. Collins, **S. N. Vogel**. Classically activated mouse macrophages produce methylglyoxal that induces a TLR4- and RAGE-independent proinflammatory response. *J. Leukoc. Biol.* (2020) doi: 10.1002/JLB.3A0520-745RR.
(*online ahead of print*)

Tonya Webb, PhD

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Personal Statement

A major focus of the research in the Webb is to delineate mechanisms regulating natural killer T (NKT) cell development and effector functions, in order to harness their potential and develop novel immunotherapeutic strategies. Other areas of interest include investigating cancer-mediated immune suppression and cancer health disparities.

Projects/Grants

01/01/19- 12/31/21 (PI: Webb)
American Cancer Society *"Institutional Research Grant"*

08/01/19- 07/31/20 (PI: Webb)
UMB/ UMGCCC Payline Grant "*Restoring anti-tumor immunity in ovarian cancer*"

11/17/19- 5/17/21 (PI: Webb)
Amgen "*Immunotherapy following R-CHOP"*

Recent Publication

Lee MS, Sun, W, **Webb TJ**. (2020) Sphingosine Kinase Blockade Leads to Increased Natural Killer T Cell Responses to Mantle Cell Lymphoma. Cells. 9(4):1030.

Shissler SC, Singh NJ, **Webb TJ**. (2020) Thymic resident NKT cell subsets show differential requirements for CD28 co-stimulation during antigenic activation. Sci Rep.10(1):8218.

Webb TJ, Yuan W, Meyer E, Dellabona P. (2020) Editorial: NKT Cells in Cancer Immunotherapy. Front Immunol. 11:1314.

Jean Yared, MD

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Personal Statement

Dr. Yared's research interests are in preventing complications during and after stem cell transplantation, reducing the rate of relapsed disease after stem cell transplantation, the role of maintenance treatment in lymphoma. Dr. Yared received a large grant to launch, as the principal investigator (PI), a multicentric investigator-initiated phase 2 clinical trial testing the role of a PI3K inhibitor maintenance treatment of indolent B-cell lymphoma after high dose chemotherapy and autologous stem cell transplantation. He is the local PI on cooperative and pharmaceutical clinical trials and he is a Co-investigator on several other clinical trials at the cancer center. Dr. Yared is an active investigator in the Center for International Blood and Marrow Transplant Research (CIBMTR) which is a working group of more than 500 transplantation centers worldwide that contribute detailed data on hematopoietic cell transplantation to a statistical center at the Medical College of Wisconsin; Dr. Yared has co-authored several observational studies conducted by the CIBMTR. Dr. Yared is also working in conjunction with the Department of Pharmaceutical Health Services Research at the University of Maryland School of Pharmacy on SEER/Medicare registry data regarding patients with multiple myeloma and lymphoma.

Recent Publications

Survival Outcomes of Allogeneic Hematopoietic Cell Transplants with EBV positive or EBV negative Post Transplant Lymphoproliferative Disorder (PTLD), A CIBMTR Study. Naik S, Riches M, Hari P, Soyoung K, Chen M, Bachier C, Shaughnessy P, Hill J, Ljungman P, Battiwalla M, Chhabra S, Daly A, Storek J, Ustun C, Diaz MA, Cerny J, Beitinjaneh A, **Yared J**, Brown V, Page K, Dahi PB, Ganguly S, Seo S, Chao N, Freytes CO, Saad A, Savani BN, Ahn KW, Boeckh M, Heslop HE, Lazarus HM, Auletta JJ, Kamble RT. Transpl Infect Dis. 2019 Jul 12:e13145. doi: 10.1111/tid.13145. [Epub ahead of print]. PMID: 31301099

Increased overall and bacterial infections following myeloablative allogeneic HCT for patients with AML in CR1. Cellatin Ustun, **Jean A. Yared**. Manuscript accepted on 6/15/19 in *Blood Advances*

Rania Younis, B.D.S., M.D.S., Ph.D.

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Personal Statement

Dr. Younis lab was the first to stratify HNSCC into 4 subgroups according to combined analysis of expression of the 2 immune biomarkers: Semaphorin 4D and Programmed death ligand 1 (PD-L1) in tumor cells, that carries significant implications in the world of personalized cancer treatment for HNSCC patients. Her lab was also the first to demonstrate a novel mechanism of tumor immune suppression: upregulation of myeloid suppressor cells and T regulatory cells, through HNSCC production of Semaphorin 4D (Sema4D). That activated TGF-β1 levels in the tumor microenvironment can be mediated downstream of Sema4D/Plexin-B1. That Sema4D can be detected in peripheral blood of HNSCC as an immune biomarker.

Projects/Grants

American Cancer Society pilot grant
Title: Semaphorin 4D induces a dense fibrotic Head and Neck cancer stroma

Department of Oncology and diagnostic Science,
SOD : Oncology general fund
Title: Semaphorin 4D role in differential response to standard immunotherapy in head and neck cancer

TEDCO-MII Phase I; Title: A blood diagnostic for assessing Head and Neck cancer Histological Immune profile.

SOD-INSPIRE: Tumor inflammation signature as a predictive biomarker of recurrence in oral squamous cell carcinoma.

Recent Publications

Combination Nivolumab/Ipilimumab Immunotherapy For Melanoma With Subsequent Unexpected Cardiac Arrest: A Case Report and Review of Literature. Khoury ZH, Hausner PF, Idzik-Starr CL, Frykenberg MRA, Brooks JK, Dyalram D, Basile JR, **Younis RH**. J Immunother. 2019 Jun 14. PMID: 31206394

Roshanak Derakhshandeh, Kyu Lee Han, Haiyan Chen, Tonya Webb, **Rania H. Younis.** Semaphorin 4D in human head and neck cancer tissue and peripheral blood: A dense fibrotic peri-tumoral stromal phenotype. *Oncotarget 2018 Jan 19;9(13):11126-11144.PMID: 29541402*

Richard Y. Zhao, PhD

Professor (Tenured)
Pathology
Microbiology and Immunology
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Personal Statement

Dr. Richard Zhao's basic science research interest is in the areas of HIV/AIDS, Zika virus and anticancer therapies. Specifically, his laboratory conducts research to study virus-host interactions, cell cycle regulation and high throughput drug screening, testing and development. Dr. Zhao uses a unique approach in his research by combining the tools of molecular biology, fission yeast (Schizosaccharomyces pombe) genetics, mammalian biology and virology into a single theme. Such a distinctive combination of tools often give rise to unique perspectives of scientific findings that are otherwise difficult to obtain based solely on a single approach or organism.

Dr. Zhao's clinical science research expertise is in the areas of gene-based diagnostics, translational genomics and individualized molecular testing for precision medicine.

Projects/Grants

Role of HIV-1 viral protein R (Vpr) in neuroinflammation and neurotoxicity of HIV-associated neurocognitive disorders

Drug discovery and testing of HIV-1 drug resistant protease inhibitors

Study of functional genome of Zika virus and SARS-CoV2/COVID-19

Recent Publications

Jin, H., et al., 2020. A novel class of plant and animal viral proteins that disrupt mitosis by directly interrupting the mitotic entry switch Wee1-Cdc25-Cdk1. *Science Advances*. 13 May, 6:20 eaba3418. DOI: 10.1126/sciadv.aba3418

Li, G., T. et al., 2020. HIV-1 Vpr-induced proinflammatory response and apoptosis are mediated through the Sur1-Trpm4 channel in astrocytes. *bioRxiv*. BIORXIV/2020/999268; doi: https://doi.org/10.1101/2020.03.19.999268.

Li G, et al., 2019. The Roles of prM-E proteins in historical and epidemic Zika virus-mediated infection and neurocytotoxicity. Viruses. 2019 Feb 14;11(2). pii: E157. doi: 10.3390/v11020157. PubMed PMID: 30769824.

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Thank you all very much.