# NIH-FDA IIG

National Institutes of Health // Food and Drug Administration // Immunology Interest Group

# NEWSLETTER

## MARCH 2024

## PUBLICATIONS

### Clinical and functional spectrum of RAC2-related immunodeficiency

Donkó A, Sharapova SO, Kabat J, Ganesan S, . . . Holland SM, Leto TL, Hsu AP.
Blood. 2024 Jan 9:blood.2023022098.
doi: 10.1182/blood.2023022098. PMID: 38194689

*We collected an international cohort of 54 patients with RAC2 mutations, identifying clinical features and performing functional studies to characterize the mutations. We defined three disease presentations that correlate with protein function: constitutively active, RAS-like cause severe combined immune deficiency, dominant-negative resemble leukocyte adhesion deficiency, dominant-activating cause a combined immune deficiency.*

### Multifaceted roles for STAT3 in gammaherpesvirus latency revealed through in vivo B cell knockout models

Hogan CH, Owens SM, Reynoso GV, Liao Y, Meyer TJ, Zelazowska MA, Liu B, Li X, Grosskopf AK, Khairallah C, Kirillov V, Reich NC, Sheridan BS, McBride KM, Gewurz BE, Hickman HD, Forrest JC, Krug LT.
mBio. 2024 Feb 14;15(2):e0299823.
doi: 10.1128/mbio.02998-23. PMID: 38170993

*Chad Hogan was a CRTA student in the Graduate Partnership Program with Stony Brook University who defended his dissertation research last year. This paper describes his application of the model pathogen murine gammaherpesvirus 68 to investigate the role of the host factor STAT3 in the establishment of gammaherpesvirus latency in B cells using mixed bone marrow chimeric models. STAT3 was required to support virus-driven proliferation and the suppression of interferon responses in the infected B cells of the germinal center.*

### Tumor resistance to anti-mesothelin CAR-T cells caused by binding to shed mesothelin is overcome by targeting a juxtamembrane epitope

Liu XF, Onda M, Schlomer J, Bassel L, Kozlov S, Tai C-H, Zhou Q, Liu W, Tsao H-E, Hassan R, Ho M,Pastan I.
PNAS. 2024 Jan 23;121(4):e2317283121.
doi: 10.1073/pnas.2317283121. PMID:38227666

*This paper describes humanized CAR-T cells that target mesothelin. They do not bind to shed mesothelin, a major barrier to antibody-based therapies, and cause complete remissions in a difficult to treat pancreatic cancer PDX model.*

### Amelioration of experimental autoimmune encephalomyelitis by in vivo reprogramming of macrophages using pro-resolving factors

Gauthier T, Martin-Rodriguez O, Chagué C, Daoui A, Ceroi A, Varin A, Bonnefoy F, Valmary-Degano S, Couturier M, Behlke S, Saas P, Cartron P, Perruche S
Cancers (Basel). 2023 Oct 8;15(19):4885.
doi: 10.3390/cancers15194885. PMID: 37835579

*Reinstating inflammation resolution represents an innovative concept to regain inflammation control in diseases marked by chronic inflammation. Here, we found that injection of the pro-resolutive secretome of macrophages in a multiple sclerosis model reduced demyelination and decreased inflammatory cell infiltration in the CNS, through the in vivo reprogramming of macrophages at the epigenetic level. These findings open a new therapeutic avenue for diseases marked by neuroinflammation.*

## Multi-omic profiling of follicular lymphoma reveals changes in tissue architecture and enhanced stromal remodeling in high-risk patients

Radtke AJ, Postovalova E, Varlamova A, Bagaev A, Sorokina M, Kudryashova O, Meerson M, Polyakova M, Galkin I, Svekolkin V, Isaev S, Wiebe D, Sharun A, Sarachakov A, Perelman G, Lozinsky Y, Yaniv Z, Lowekamp BC, Speranza E, Yao L, Pittaluga S, Shaffer III AL, Jonigk D, Phelan JD, Davies-Hill T, Huang DW, Ovcharov P, Nomie K, Nuzhdina E, Kotlov N, Ataullakhanov R, Fowler N, Kelly M, Muppidi J, Davis JL, Hernandez JM, Wilson WH, Jaffe ES, Staudt LM, Roschewski M, Germain RN
Cancer Cell 2024 Mar 11;42(3):444-463.e10.
doi: 10.1016/j.ccell.2024.02.001. PMID: 38428410

*NIH investigators, in collaboration with BostonGene, utilize advanced sequencing and imaging technologies to characterize the tumor microenvironment of follicular lymphoma patients. Data integration reveals tumor-specific features and microenvironmental patterns enriched in high-risk patients. IBEX, one of the imaging methods used in this study, is an open source technique developed by NIAID investigators.*

## Generation of murine tumor models refractory to PD-1/-L1 therapies due to defects in antigen processing/ presentation or IFN signaling using CRISPR/Cas9

Chariou PL, Minnar CM, Tandon M, Guest MR, Chari R, Schlom J, Gameiro SR
PLoS ONE. 2024 Mar 1;19(3): e0287733.
doi:10.1371/journal.pone.0287733. PMID: 38427670

*The development of a CRISPR/Cas9 approach to generate murine tumor models refractory to PD-1/-L1 inhibition opens up the possibility of the systematic study of gene deletions promoting PD-1 or PD-L1 immune checkpoint blockade due to antigen processing/presentation machinery and interferon gamma signaling mutations. This in turn will help facilitate the discovery of alternative treatment options and a deeper understanding of the immune consequences of tumor mutations, with potential clinical implications.*

## Blood-based biomarkers in patients with non-small cell lung cancer treated with immune checkpoint blockade

Tsai Y, Schlom J, Donahue RN
J. Exp Clin. Cancer Res. 2024 March 16;43(1):82.
doi: 10.1186/s13046-024-02969-1. PMID: 38493133

*Despite many obstacles, combining multiple assays in peripheral blood or integrating them with traditional clinical factors, each of which holds its own promise in identifying correlates of clinical response, has the potential to improve the ability of clinicians to identify those patients who may best respond to a given therapy. While this review focused on promising advances in the field of blood-based biomarkers in non-small cell lung cancer patients treated with immune checkpoint inhibitors, the blood-based assays described are not cancer specific and could be considered more widely for application in immunotherapy studies of all solid tumors.*

## Recent Advancements in Subcellular Proteomics: Growing Impact of Organellar Protein Niches on the Understanding of Cell Biology

Bhushan V, Nita-Lazar A
J Proteome Res. 2024 Mar 7.
doi: 10.1021/acs.jproteome.3c00839. PMID: 38451675

*This is a review providing a comprehensive repository for recent advancements in subcellular proteomics subcontexting methods, challenges, and future perspectives for method developers. We discuss recent advancements in mass spectrometry, imaging technology, computational tools, and deep machine learning algorithms, and give examples of studies pertaining to subcellular protein localization and their dynamic distributions*

## Lipopolysaccharide Regulates the Macrophage RNA-Binding Proteome

Rathore D, Marino MJ, Issara-Amphorn J, Hwan Yoon S, Manes NP, Nita-Lazar A
J Proteome Res. 2024 Mar 25.
doi: 10.1021/acs.jproteome.3c00838. PMID: 38527097

*To examine the changes in the RNA binding subproteome in mouse macrophages in response to LPS we used SILAC labeling for quantification, combined it with modified TRAPP protocol, which captures proteins bound to all RNA types in an unbiased manner utilizing UV-radiation-based crosslinking, and analyzed using high resolution mass spectrometry. We have reproducibly identified and quantified a total of 584 RBPs at all timepoints, showing that most of the RBPs dissociate from RNA already after 30 minutes of LPS exposure and that this dissociation was independent of changes in gene expression and protein abundance.*


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## Omicron Spike confers enhanced infectivity and interferon resistance to SARS-CoV-2 in human nasal tissue

Shi G, Li T, Lai KK, Johnson RF, Yewdell JW, Compton AA
Nat Commun. 2024 Jan 30;15(1):889.
doi: 10.1038/s41467-024-45075-8. PMID: 38291024

*We show that mutations unique to Spike enabled Omicron sublineages to gain infectivity in human upper airway epithelium, and this was associated with a unique dependence on cellular metalloproteinases for Spike-mediated membrane fusion. This entry pathway also confers resistance to the antiviral state induced by type-I and type-III interferons.*

## A bivalent Adenovirus-Vectored Vaccine induces a robust humoral response, but does not protect cynomolgus macaques against a lethal challenge with Sudan virus

van Tol S, Fletcher P, Feldmann F, Mukesh RK, Port JR, Gallogly S, Schulz JE, Rhoderick JF, Makinson R, Carmody A, Myers L, Lovaglio J, Smith BJ, Okumura A, Shaia C, Saturday G, Marzi A, Lambe T, Munster VJ, van Doremalen N
J Infect Dis. 2024 Mar 15:jiae056.
doi: 10.1093/infdis/jiae056. PMID: 38487996

*The protective efficacy of ChAdOx1-biEBOV, a vaccine encoding the GP of Ebola virus and Sudan virus, was evaluated in cynomolgus macaques using a prime or prime-boost regimen. While vaccination induced adaptive immune responses, including IgG and neutralizing antibodies, no significant difference in survival outcomes was observed upon challenge with SUDV among the vaccinated and control groups.*

## Protective human monoclonal antibodies target conserved sites of vulnerability on the underside of influenza virus neuraminidase

Lederhofer J, Tsybovsky Y, Nguyen L, Raab JE, Creanga A, Stephens T, Gillespie RA, Syeda HZ, Fisher BE, Skertic M, Yap C, Schaub AJ, Rawi R, Kwong PD, Graham BS, McDermott AB, Andrews SF, King NP, Kanekiyo M.
Immunity. 2024 Mar 12;57(3):574-586.e7.
doi: 10.1016/j.immuni.2024.02.003. PMID: 38430907

*Influenza neuraminidase (NA) is underappreciated as a vaccine target owing to its incomplete epitope landscape. Lederhofer et al. isolated human monoclonal antibodies to NA underside (i.e., dark side) epitopes with broad cross-reactivity across N2 subtype and protective efficacy in pre- and postexposure settings, providing insights for NA-based vaccine design..*

## HIV vaccines induce CD8+ T cells with low antigen receptor sensitivity

Migueles SA, Nettere DM, Gavil NV, Wang LT, Toulmin SA, Kelly EP, Ward AJ, Lin S, Thompson SA, Peterson BA, Abdeen CS, Sclafani CR, Pryal PF, Leach BG, Ludwig AK, Rogan DC, Przygonska PA, Cattani A, Imamichi H, Sachs A, Cafri G, Huang N, Patamawenu A, Liang CJ, Hallahan CW, Kambach DM, EX, Coupet T, Chen J, Moir SL, Chun T, Coates EE, Ledgerwood J, Schmidt J, Taillandier-Coindard M, Michaux J, Pak H, Bassani-Sternberg M, Frahm N, McElrath MJ, Connors M
Science. 2023 Dec 15;382(6676):1270-1276.
doi: 10.1126/science.adg0514. PMID: 38096385

*Current HIV vaccines designed to stimulate CD8+ T cells induce cells with poor cytotoxic capacity and low functional avidity. These HIV-specific CD8+ T cell TCRs were of insufficient sensitivity to cause degranulation in response to the low peptide-MHC on HIV-infected CD4+ T cells.*

## Lysosomal processing of sulfatide analogs alters target NKT cell specificity and immune responses in cancer

Nishio K, Pasquet L, Camara K, DiSapio J, Hsu KS, Kato S, Bloom A, Richardson SK, Welsh JA, Jiang T, Jones JC, Cardell S, Watarai H, Terabe M, Olkhanud PB, Howell AR, Berzofsky JA
J Clin Invest. 2023 Dec 21;134(4):e165281.
doi:10.1172/JCI165281. PMID: 38127463

*The paper describes the first case in which antigen processing changes the type of T cell responding rather than affecting ability to load the MHC molecule. A lipid antigen that normally stimulates suppressive type II NKT cells when presented without processing is processed by DCs to a form that stimulates immuno-protective type I NKT cells instead, reversing the function. Both forms load onto CD1d, the class I MHC-like presenting molecule, so the processing does not affect loading.*

## A pathway linking atopic dermatitis to skin microbes

Zhu J
Cell Host Microbe. 2024 Feb 14;32(2):154-155.
doi: 10.1016/j.chom.2024.01.009. PMID: 38359797

*Interactions between microbiota and host skin have an important impact on cutaneous immunity and inflammation. In this issue of Cell Host & Microbe, Cha et al. report that skin commensal bacteria-mediated priming of group 2 innate lymphoid cells in early life predisposes the mice to atopic dermatitis-like inflammation in adulthood.*


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## C1q enables influenza hemagglutinin stem binding antibodies to block viral attachment and broadens the antibody escape repertoire

Kosik I, Da Silva Santos J, Angel M, Hu Z, Holly J, Gibbs JS, Gill T, Kosikova M, Li T, Bakhache W, Dolan PT, Xie H, Andrews SF, Gillespie RA, Kanekiyo M, McDermott AB, Pierson TC, Yewdell JW
Sci Immunol. 2024 Mar 22;9(93):eadj9534.
doi: 10.1126/sciimmunol.adj9534. PMID: 38517951

*Despite their failure to impede viral attachment, broadly neutralizing anti-hemagglutinin stem antibodies hold promise for the development of a universal influenza vaccine. Our research reveals that the presence of complement protein C1q promotes a novel mechanism of action, inhibiting attachment and broadening the viral escape repertoire to encompass the globular HA head domain.*

## Epithelial-derived interleukin-23 promotes oral mucosal immunopathology

Kim TS, Ikeuchi T, Theofilou VI, Williams DR, Greenwell-Wild T, June A, Adade EE, Li L, Abusleme L, Dutzan N, Yuan Y, Brenchley L, Bouladoux N, Sakamachi Y, NIDCD/NIDCR Genomics and Computational Biology Core, Palmer Jr RJ, Iglesias-Bartolome R, Trinchieri G, Garantziotis S, Belkaid Y, Valm AM, Diaz PI, Holland SM, Moutsopoulos NM
Immunity. 2024 Mar 19:S1074-7613(24)00096-7.
doi: 10.1016/j.immuni.2024.02.020. PMID: 38513665

*Epithelial cells at mucosal surfaces provide a structural barrier and an immune defense system, but dysregulated epithelial responses can contribute to disease. Kim et al. reveal that epithelial-derived IL-23 is a pathogenic trigger in the oral mucosal disease periodontitis. Moreover, their findings suggest a broader role for epithelial-derived IL-23 in human Th17-mediated inflammatory diseases across barrier tissues.*

## Microbial ligand-independent regulation of lymphopoiesis by NOD1

Iwamura C, Ohnuki H, Flomerfelt FA, Zheng L, Carletti A, Wakashin H, Mikami Y, Brooks SR, Kanno Y, Gress RE, Tosato G, Nakayama T, O'Shea JJ, Sher A, Jankovic D.
Nature Immunology 2023 Dec;24(12):2080-2090.
doi: 10.1038/s41590-023-01668-x. PMID: 37957354

*In this report we reveal a new function for NOD1 in regulating cytokine-induced STAT5 signaling that our evidence argues is independent of its sensing of microbial ligands.*

## Co-Imaging of RelA and c-Rel Reveals Features of NF-B Signaling for Ligand Discrimination

Rahman S, Jiang K, Singh A, Aqdas M, Hoffmann A, Sung M.
Cell Rep. 2024 Mar 26;43(3):113940.
doi: 10.1016/j.celrep.2024.113940. PMID: 38483906

*Rahman et al. performed quantitative live-imaging of macrophages from NF-B double knock-in reporter mice and show that both RelA and c-Rel subunits contribute to accurate discrimination of pathogen-derived ligands. Signaling features of the two NF-B subunits are temporally coordinated and non-redundant in individual cells.*

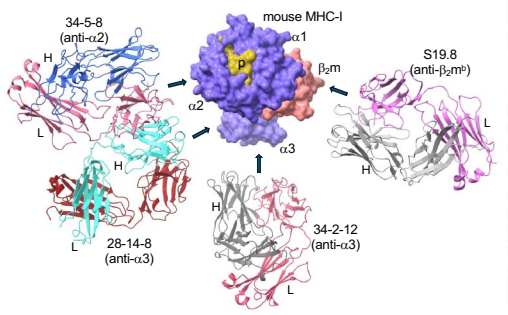
## Depleting myeloid-biased haematopoietic stem cells rejuvenates aged immunity

Ross JB, Myers LM, Noh JJ, Collins MM, Carmody AB, Messer RJ, Dhuey E, Hasenkrug KJ, Weissman IL
Nature. 2024 Mar 27.
doi: 10.1038/s41586-024-07238-x. PMID: 38538791

*To explore a potential therapeutic strategy to enhance the aged immune response, we first identified surface antigens on myeloid-biased haematopoietic stem cells (my-HSCs), as there is an age-related increase of my-HSCs over the balanced-HSCs that predominate in youth and give rise to a balanced output of lymphoid and myeloid cells necessary for optimal immunity. Aged mice were then given a cocktail of antibodies to deplete the my-HSCs which: significantly rebalanced the HSC progenitor cells in the bone marrow, increased circulating naïve T cells and mature B cells, partially restored the exhausted/age-associated phenotype of adaptive cells, reduced some inflammatory mediators in the plasma and enhanced functional immunity upon vaccination and challenge with a retrovirus.*

## Experimental Structures of Antibody/MHC-I Complexes Reveal Details of Epitopes Overlooked by Computational Prediction

Boyd LF, Jiang J, Ahmad J, Natarajan K, Margulies DH
J Immunol. 2024 Mar 8:ji2300839.
doi: 10.4049/jimmunol.2300839. PMID: 38456672





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# IIG members elected to AAI Committees

## Awards Committee 2024-2027

### Pam Schwartzberg, M.D., Ph.D.

Senior Investigator, Laboratory of Immune System Biology—National Institute of Allergy and Infectious Diseases and National Human Genome Research Institute, NIH

## Program Committee 2024-2027

### Katrin Mayer-Marber, Ph.D.

Tenure-Track Investigator, Lab of Clinical Immunology and Microbiology—National Institute for Allergy and Infectious Diseases, NIH



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# HIGHLIGHTS

The IIG annual retreat has always been an experience of joy and scientific inspiration for the IIG family of immunologists. We are happy to highlight these exciting moments captured at the past IIG retreat 2024

# Immunology Interest Group SPOTLIGHT

**Dr. Amiran Dzutsev is a Stadtman Tenure-Track Investigator in the Laboratory of Integrative Cancer Immunology at NCI/CCR. To learn more about his work, visit: https://ccr.cancer.gov/staff-directory/amiran-k-dzutsev**

Amiran Dzutsev, M.D., Ph.D.

***Tell us about your science.***

My current research interests lie in investigating the role of the microbiota in cancer therapy outcomes. It's no longer surprising that our gut microbiota influences many aspects of our health, and this effect also extends to its significant impact on the outcomes of various cancer therapies, ranging from traditional chemotherapy and radiotherapy to more contemporary approaches like immune checkpoint inhibitors and CAR T-cell therapies.

Over the past decade, there has been a proliferation of studies investigating the impact of gut microbiota on cancer therapy outcomes, stemming from initial observations made by our group and several others. Additionally, numerous clinical studies and biotech startups have emerged aiming to leverage the microbiome to enhance the efficacy of cancer therapies. Indeed, recent clinical investigations, including our own, suggest that the microbiome may exert control over approximately 50-70% of the efficacy of certain cancer treatments. In fact, our group and several others have demonstrated that fecal microbial transfer (FMT) in melanoma cancer patients results in a dramatic increase in the efficacy of anti-PD1 therapy. The ultimate goal in this field is the identification of the precise mechanisms by which the microbiome influences cancer therapy. However, despite significant progress in this direction, pinpointing molecular drivers from both the microbiome and the host side remains elusive.

Our research group is also delving into the relatively new field of studying the composition of intratumoral microbiota and its role in cancer development and therapy outcomes. It has become evident that many tumors harbor a small yet significant population of microbes. Some of these intratumoral microbes are transient, just passing through and becoming trapped in enlarged blood vessels within the tumor. Others actively attempt to survive and proliferate within the tumor microenvironment, often evading the immune system by hiding within tumor cells. Both types of microorganisms likely influence intratumoral immune cells and, consequently, the immune response to the tumor. While there is supporting evidence in the literature, the field still struggles with methodological challenges, making premature conclusions likely.

***What event(s) lead to your career in science and interest in immunology?***

I was always interested in science, but I would say that I seriously started considering science as a carrier in a medical school, where during my second or third year together with my friend, and completely on our own, we developed our first research project, that studied the impact of industrial contaminants on development of cancers. We found completely naively, without referring to the literature, that Cadmium increases the risk of breast cancer in women, and that was such an invigorating feeling of a true discovery that it sparked my interest in biomedical research and changed my life.

***How has a mentor or colleague substantially influenced your career trajectory?***

I've been fortunate to be influenced by many great minds who guided me through the complicated and convoluted world of science, helping me develop a fascination for the real world of science that lies behind what we see and feel around us. They also cultivated my critical scientific thinking skills, which I now use as a tool in my day-to-day work. My latest research trajectory, studying the relationship between cancer and the microbiome, is owed to Giorgio Trinchieri. In his lab, we embarked on a journey of discovery regarding the role of commensal microbes in health and disease. He taught me not only to grapple with complex new types of research and methodologies by dissecting things into more manageable pieces, but also how to pay attention to minute details while keeping the big picture in mind, and to constantly question all assumptions to get the


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most out of the data on hand.

***In what area(s) do you expect significant research/medical advances in the next 5-10 years?***
We are all acutely aware that we live in the era of the AI revolution, so undoubtedly, sooner rather than later, we will see its ripple effects reach us in a major way. We can only guess at the specifics - from data analysis to hypothesis generation and paper writing. One thing is certain – it will greatly accelerate the process of discovery. Furthermore, many novel technology-driven discoveries await us, as single-cell sequencing, spatial transcriptomics, and metabolomics become widely available to people across the world. Another game-changing technology with high hopes is direct protein sequencing with Oxford Nanopore, which is also about to hit the market. Additionally, the combination of AI with our enhanced ability to rapidly synthesize any gene gives us a completely new outlook on what is possible in synthetic biology, from generating novel types of immunotherapeutics to creating new types of molecules and cells with properties that have never existed in nature before. As these advancements converge, we stand on the brink of an exciting era of innovation and discovery.

***What do you value most about the NIH-FDA Immunology community?***
I think here at NIH we are fortunate to have some of the greatest minds in immunology concentrated in one place in an amount that you might call a critical mass—a concentration at which you have a self-sustaining fire of scientific discovery. We have people who are experts in almost every field of immunology, and no matter how unusual and rare expertise you might require help with, there is almost certainly someone here at NIH/FDA to consult with. Here we also enjoy weekly talks by some of the best scientists in the world and have retreats where we get to see each other and talk science. However, I do feel that we lack round tables where we could have open discussions about the problems, challenges, or big unanswered questions in immunology.


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# Immunology Interest Group

# SPOTLIGHT

**Dr. Karen Elkins is a Senior Investigator and Associate Director for Science at Center for Biologics Evaluation and Research at FDA.**

***What sparked your interest in science, and how did you choose your area of research/scientific questions at different stages of your career?***

Karen Elkins, Ph.D.

Looking back, I see now how heavily influenced I was by some spectacular teachers. In 4th grade, one wonderful teacher had the whole class participate in a hands-on experiment every Monday, and that did it for the experimental science path. In high school, the world's greatest biology teacher led to me love everything about living organisms, and in college a super cell biology instructor focused me on the joy of cells. By the time I went to grad school, I was aiming for cell-cell communication research, when a captivating immunology professor made it clear that all of immunology and microbiology were basically nothing but inter-cell communication. That sealed the deal! I guess I'm pretty suggestible.

Beyond the appeal of a topic area, years ago my husband the virologist taught me my favorite approach to choosing scientific questions. He phrased in terms of what not to do: scientists too often ask trivial questions, or ask questions just because they can. The concept seems obvious, but it's amazing to me how many really bright people go off on trivial tangents. When I get fired up about an experiment, I try to step back and think – is this addressing something really important and it is really worth doing??

***In what area(s) do you expect significant research/medical advances in the next 5-10 years?***

I think part of the major advances are basically already on the doorstep: the recent explosion of success in gene and cell therapies is amazing, and it's thrilling. I also have hope for some serious progress in treating some major neurological diseases (even if that's a bit of wishful thinking and self-interest).

***What do you feel is one of the most challenging events in your career, and how did you cope with the difficulty?***

Virtually no scientist gets properly trained in managing people, and my biggest challenge came when a team member developed substantial behavioral and emotional difficulties. Those changes really impacted the work and the rest of the lab. I didn't cope well at all, until I did something we're also not well trained to do: I asked for help. Once I asked, I got great support and practical guidance from both the institution and from my colleagues and my bosses. Moral: you don't have to go it alone.

***Could you share your mentoring experience? What do you think contributed to the fulfillment of your mentorship?***

What a hard question. I've had fabulous mentors and I've always felt a great responsibility to be a mentor to others, but I've worried all my professional life that I'm just not good at it. All I can say is that I've tried to be available to people around me to talk and listen, at whatever level someone seems to want.

***The covid pandemic reminded us of the importance of science literacy among the general public. What do you think we could do to help improve science education?***

Oh, my goodness, so much is needed! For starters, I think science education in many public schools is nowhere near where it should be, and we need to advocate for better resources for hands-on science and experiential opportunities.



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***How to you spend your free time? What time management experience you would like to share?***

Going backwards, maybe the best advice I ever got long ago was to be willing to pay for household services. Getting over trying to be my own plumber was the only way I actually had free time to spend! So, we've always budgeted to pay experts for help, and instead I can just hang out with my wonderful husband, cook, and hike with our dogs. I love all forms of music and reading, and at an advanced age, I took up playing the cello (twinkle, twinkle has nothing on me now).

***What advice would you like to give to the NIH/FDA immunologist community?***

We are all so, so fortunate to be working in this field and at these wonderful places. ENJOY IT!!! Relish both the remarkable science and the rich relationships that are all around us. Share the joy of discovery. Collaborate widely and generously. Aim for excellence every day. Make a contribution to science and to others – even if you're an introvert, put yourself out there on behalf of your lab, your colleagues, and your scientific community.


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# Bench-to-Bedside in Action

## Translating immunology to transform clinical care

Harnessing fundamental knowledge to advance our understanding of disease and develop novel treatment strategies is a major mission of the NIH. Each month we highlight interesting clinical trials taking place at the NIH Clinical Center that are doing just that.

**Pacritinib, a JAK2/IRAK1 inhibitor for kaposi sarcoma herpesvirus linked diseases.** PI: Ramya Ramaswami, M.B.B.S., M.P.H. – Lasker CLinical Research Scholar, HIV and Malignancy Branch, NCI,/CCR, DIR.

**Background:** Kaposi sarcoma herpesvirus (KSHV) is the causative agent for several conditions, including Kaposi sarcoma (KS), a lymphoproliferative disorder - multicentric Castleman disease (MCD) and an inflammatory cytokine disorder KICS. Both KICS and MCD associate with elevated interleukin-6 (IL6) and can occur with concurrent KS. Existing treatment for MCD and KICS includes rituximab, a monoclonal antibody against CD20+ B cells. The rituximab response rate in MCD is approximately 80%. However, up to 20% of patients experience flares with associated inflammatory symptoms. Furthermore, why rituximab has efficacy in MCD is unclear as MCB plasmablasts are CD20-negative. Moreover, rituxibab associated immunosuppression can worsen existing KS in these patients. We investigated use of tocilizumab, an anti-IL6 receptor (gp80) monoclonal antibody in MCD. However, the response rate for tocilizumab alone was 63% with a response duration limited to 3.2 months. Similar to rituximab, we noted worsening of KS and the onset of KS among study participants treated with tocilizumab. The limited responses seen in the tocilizumab was likely due to the effect of the effect of a vIL6 in MCD, the viral homolog of human IL6, which signals through the gp130 receptor of IL6, without requiring gp80. The Yarchoan Lab studied several JAK/STAT inhibitors and identified Pacritinib, a JAK2/IRAK1 inhibitor which reduced KSHV viability in a lymphoma cell lines.

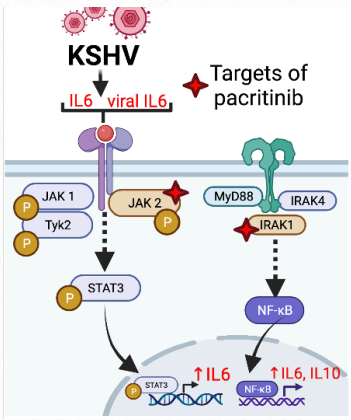


**Fig 1.** Schematic of targets of pacritinib to attenuate KSHV inflammatory signaling.

**Hypothesis:** We hypothesize that Pacritinib, a JAK2/IRAK1 inhibitor will alter the natural history of signs and symptoms associated with KAD among patients with MCD and KICS.

**Study Design:** A phase II study powered to examine the activity and clinical benefit of Pacritinib. Participants will be divided into three cohorts. Cohort 1 and 2 will include MCD participants, divided by prior therapy. Cohort 3 includes participants with KICS. Participants may or may not have a diagnosis of concurrent KS. Therefore, we will be able to evaluate the effect of this therapy on a spectrum of KAD conditions. With this study, we expect to investigate this class of JAK/STAT inhibitors in KSVH associated diseases, which will be important progress for patients with MCD and KICS with or without concurrent KS.

**What we hope to learn:** (i) What is the response to Pacritinib in MCD and KICS using the Clinical Benefit Response (CBR) Criteria? (ii) How does pacritinib change circulating inflammatory cytokines and how does this correlate with response? (iii) How do baseline tissue (KS and lymph node) JAK2 and IRAK1 expression levels and KSHV infection correlate with Pacritinib response? What are the other genes in the JAK/STAT and IRAK/NF-kB signaling pathway that are activated in these tissues that are the associated cell types and KSHV infection status?



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# Immunology Interest Group
# SEMINAR SERIES

## *Upcoming seminars*

### April 2024

April 3, 2024
**Chris Hunter (Upenn)**
Host: Roxane Tussiwand

April 10, 2024
**Betty Diamond (Feinstein)**
Host: Rachel Caspi

April 17, 2024
**Daniel Kaplan (Pittsburgh)**
Host: Alexandria Wells

April 24, 2024
**Manolis Pasparakis (Cologne)**
Host: Christian Mayer

### May 2024

May 1, 2024
**Polly Matzinger (NIAID)**
Host: Amy Hsu

May 15, 2024
**De'Broski R. Herbert (Upenn)**
Host: P'ng Loke

May 22, 2024
**Andrea Reboldi (UMass)**
Host: Jagan Muppidi

May 29, 2024
**Richard Grencis (Manchester)**
Host: Oyebola Oyesola

### June 2024

June 5, 2024
**Ivan Zanoni (Harvard)**
Host: Michail Lionakis

June 26, 2024
**Caroline Sokol (Harvard)**
Host: Ron Germain

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*Recordings are generally available 1-2 weeks after the presentation.

Note: Dr. Helen Su (NIAID) presented the IIG Seminar on February 14, 2024 in place of Dr. Thirumala-Devi Kanneganti (St. Jude).



Continued>>

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