NIH-FDA IIG

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NEWSLETTER

MARCH 2023

PUBLICATIONS

Immune responses to human fungal pathogens and therapeutic prospects

Lionakis MS, Drummond RA, Hohl TM.
Nat Rev Immunol. 2023; 1-20. doi: 10.1038/s41577-022-00826-w.
DOI: 10.1038/s41577-022-00826-w, PMID: 36600071, PMCID: PMC9812358

This review provides a mechanistic synthesis of host defenses against medically important fungi.

IFN-γ and TGF-β, Crucial Players in Immune Responses: A Tribute to Howard Young

Gauthier T, Chen W.
J Interferon Cytokine Res. 2022 Dec;42(12):643-654.
PMID: 36516375 PMCID: PMC9917322 (available on 2023-12-01) DOI: 10.1089/jir.2022.0132

Interferon gamma (IFN-γ) and transforming growth factor beta (TGF-β), both pleiotropic cytokines, have been long studied and described as critical mediators of the immune response. One of the investigators who made seminal and critical discoveries in the field of IFN-γ biology is Dr. Howard Young. In this review, we provide an overview of the biology of IFN-γ as well as its role in cancer and autoimmunity with an emphasis on Dr. Young's critical work in the field; and we describe how Dr. Young's work influenced our own research studying the role of TGF-β in the modulation of immune responses.

Small-molecule screening identifies Syk kinase inhibition and rutaecarpine as modulators of macrophage training and SARS-CoV-2 infection

John SP, Singh A, Sun J, Pierre MJ, Alsalih L, Lipsey C, Traore Z, Balcom-Luker S, Bradfield CJ, Song J, Markowitz TE, Smelkinson M, Ferrer M, Fraser IDC
Cell Rep. 2022 Oct 4; 41(1): 111441.
PMID: 36179680 PMCID: PMC9474420 DOI: 10.1016/j.celrep.2022.11144

Two new trained immunity stimuli were identified using a small molecule screen. Training of macrophages with Syk inhibition with multiple Syk inhibitors including fostamatinib, an FDA approved drug, led to the inhibition of Influenza virus, OC43 coronavirus and multiple variants of SARS CoV2.

CD47-Dependent Regulation of Immune Checkpoint Gene Expression and MYCN mRNA Splicing in Murine CD8 and Jurkat T Cells

Kaur, S., Awad, D., Finney, R. P., Meyer, T. J., Singh, S. P., Cam, M. C., Karim, B. O., Warner, A. C., and Roberts, D. D.
Int. J. Mol. Sci. 2023, 24(3), 2612.
PMID: 36768931 PMCID: PMC9916813 DOI: 10.3390/ijms24032612

Investigating transcriptome changes during T cell activation in vitro using mouse CD8 T cells and human Jurkat T lymphoblasts established that the CD47 signaling ligand thrombospondin-1 inhibits the induction of MYCN, TIGIT, CD40LG, and MCL1 mRNAs in a CD47-dependent manner. Although melanoma cells do not express MYCN, expression of MYCN, but not MYC or MYCL, in melanomas in The Cancer Genome Atlas was positively correlated with overall survival and with CD47-dependent markers of T cell activation.

Why do humans need thrombospondin-1?

Kaur S, Roberts DD.
J Cell Commun Signal. 2023 Jan 23. doi: 10.1007/s12079-023-00722-5.
PMID: 36689135 DOI: 10.1007/s12079-023-00722-5

A significant deficit in loss of function mutants for the THBS1 gene in 150,000 healthy human genomes in The Genome Aggregation Database indicated that thrombospondin-1 serves an essential function, but knockout mice indicated that this gene is not essential for mammalian embryonic development or adult reproduction. However, stress response models using transgenic mice have identified protective functions of thrombospondin-1

and some of its receptors in the cardiovascular system and immune defenses that could account for its intolerance to loss of function mutants in humans.

Analysis of tumor-immune functional responses in a mathematical model of neoantigen cancer vaccines.

Han L, Rodriguez Messan M, Yogurtcu ON, Nukala U, Yang H
Math Biosci. 2023.
PMID: 36642160 DOI: 10.1016/j.mbs.2023.108966

This paper analyzed two widely used functional forms that represent the killing rate of tumor cells by immune cells in a simple mathematical model. The different biological implications resulting from the two functional forms are highlighted.

TGF-β Regulation of T Cells

Chen W
Annual Review of Immunology 2023, Vol. 41: 483-512
PMID: 36750317 DOI: 10.1146/annurev-immunol-101921-045939

TGF-β is a key cytokine regulating the development, activation, proliferation, differentiation, and death of T cells. TGF-β also regulates the generation or function of natural killer T cells, T cells, innate lymphoid cells, and gut intraepithelial lymphocytes. In this review article, I highlight the major findings and recent advances in our understanding of TGF-β regulation of T cells and provide a personal perspective of the field

B cell receptor-induced IL-10 production from neonatal mouse CD19+CD43- cells depends on STAT5-mediated IL-6 secretion

Sakai J, Yang J, Chou CK, Wu WW, Akkoyunlu M.
Elife. 2023 Feb 3;12:e83561.
doi: 10.7554/eLife.83561.
PMID: 36735294 PMCID: PMC9934864 DOI: 10.7554/eLife.83561

This study demonstrates that neonatal mice produce more CD43- B cell-derived IL-10 following anti-BCR stimulation than adult mice. This is due to a unique neonatal specific mechanism whereby anti-BCR stimulated neonatal CD43- B cell IL-10 production is dependent on pSTAT5 mediated IL-6 secretion, which in turn enhances IL-10 production via pSTAT3.

Not too little, not too much: The impact of mutation types in Wiskott-Aldrich Syndrome and RAC2 patients

Hsu, A.P.
Clin Exp Immunol. 2023 Jan 6;uxad001.
doi: 10.1093/cei/uxad001. PMID: 36617178 DOI: 10.1093/cei/uxad001

This review examines genotype-phenotype correlations in patients with WAS (Wiskott-Aldrich Syndrome) and RAC2 mutations, highlighting functional protein domains, how mutations alter protein interactions, and how specific mutations can affect isolated functions of the protein leading to disparate phenotypes.

Differing Interpretations of RAC2 p.G15D Function

Hsu, A.P.
Clin Exp Immunol. 2023 Mar 18. doi: 10.1007/s10875-023-01471-1.
PMID: 36933077 DOI: 10.1007/s10875-023-01471-1

Two recent papers reported the same RAC2 mutation, G15D, and arrived at opposite functional conclusions. This paper points out the duplication of publication and reinterprets the data from the second manuscript to demonstrate the mutation is, in fact, an activating mutation leading to an atypical SCID presentation.

Neutrophil extracellular trap-associated carbamylation and histones trigger osteoclast formation in rheumatoid arthritis

O'Neil, L.J., Oliveira, C.B., Wang, X., Navarrete, M., Barrera-Vargas, A., Merayo-Chalico, J., Aljahdali, R., Aguirre-Aguilar, E., Carlucci, P., Kaplan, M.J. and Carmona-Rivera, C. Ann Rheum Dis. 2023 Feb 3;ard-2022-223568.
PMID: 36737106 DOI: 10.1136/ard-2022-223568

Highly carbamylated neutrophil extracellular traps (NETs) present in rheumatoid arthritis (RA) patients trigger a novel accelerated form of osteoclastogenesis (OC). NET-mediated OC depend on the activation of TLR-4 by NET-associated histone H3, neutrophil elastase, DNA and carbamylation. Our results help understanding the role of carbamylation in RA and its association with worse bone resorption.

Crosstalk between ILC2s and Th2 cells varies among mouse models

Gurram RK, Wei D, Yu Q, Butcher MJ, Chen X, Cui K, Hu G, Zheng M, Zhu X, Oh J, Sun B, Urban JF Jr, Zhao K, Leonard WJ, Zhu J.
Cell Rep. 2023 Feb 2;42(2):112073.
doi: 10.1016/j.celrep.2023.112073.
PMID: 36735533 DOI: 10.1016/j.celrep.2023.112073

ILC2s and Th2 cells are involved in various type 2 immune responses. Using novel mouse strains specifically deficient for ILC2s and Th2 cells, Gurram et al. report that the crosstalk between ILC2s and Th2 cells varies among mouse models and is mediated by type 2 alarmins and IL-4.

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Announcement of 2022 AAAS Fellows | American Association for the Advancement of Science (AAAS)

List of 2022 AAAS Fellows. **The IIG members are listed in bold text.** Congratulations to all inductees:

Karen Faith Berman, NIH National Institute of Mental Health
Linda S. Birnbaum, NIH National Institute of Environmental Health Sciences
Cynthia E. Dunbar, NIH National Heart, Lung, and Blood Institute
Eric A. Engels, NIH National Cancer Institute
Elodie Ghedin, NIH National Institute of Allergy and Infectious Diseases
Pu Paul Liu, NIH National Human Genome Research Institute
Christopher J. McBain, NIH Eunice Kennedy Shriver National Institute of Child Health and Human Development
Lee Scott Weinstein, NIH National Institute of Diabetes and Digestive and Kidney Diseases
Carmen J. Williams, NIH National Institute of Environmental Health Sciences
Howard A. Young, NIH National Cancer Institute

NCI Fellow selected for the NIH K99-R00

Congratulations!

Dr. Enitome "Tome" Bafor, a post-doctoral fellow working to understand reproductive dysfunction in the context of autoimmunity and cancer in the Cancer Innovation Laboratory (CIL), NCI/CCR, led by Howard A. Young, Ph.D. has been selected for the K99-R00 program. The NIH K99/R00 program is a pathway to independence award that provides outstanding postdoctoral scientists the opportunity to receive mentored and independent research support. The award provides up to 5 years of support within two phases.

New IIG Members

Welcome aboard!

Dr. Shen-Huan Liang joined Dr. Michail Lionakis' lab as a postdoctoral fellow in January 2023. Dr. Liang completed her PhD in Pathobiology at Brown University, specializing in fungal genetics and pathogenesis in Candida albicans. Dr. Liang is awarded the Rocky Mountain-Bethesda Fellowship 2023, under the auspices of which she will collaborate with Dr. Catharine Bosio's lab to study the regulatory roles of lipid mediators during systemic candidiasis.

Dr. Lucas Dos Santos Dias joined Dr. Michail Lionakis' lab as a staff scientist in January 2023. Dr. Dos Santos Dias obtained his PhD from Brazil and did post-doctoral research fellowship at the University of Wisconsin with Dr. Bruce Klein where he focused on the development of fungal vaccines and mechanisms of T cell-mediated antifungal. At NIAID, Dr. Dos Santos Dias will work on various projects related to mechanisms of antifungal immunity and autoimmunity.

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IIG-FAES Symposia: Barrier Immunity

November 15–17, 2023
Natcher Conference Center - BG 45

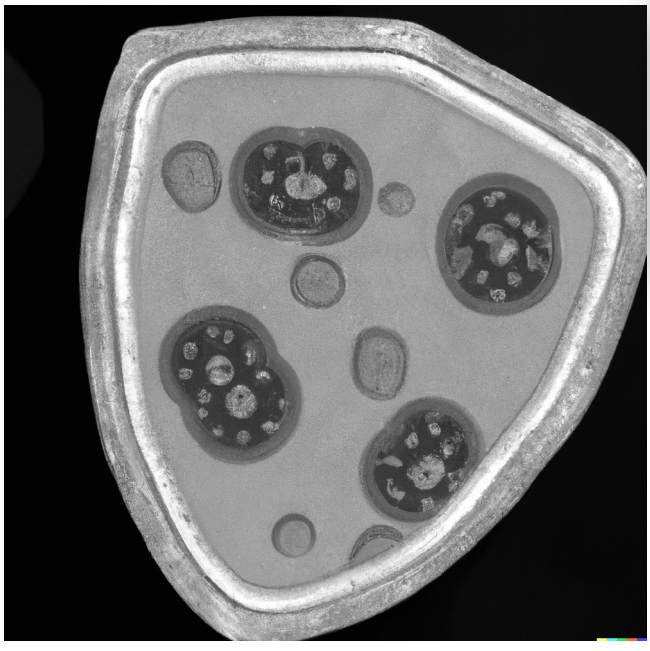
The IIG committee are excited to announce the inauguration of a brand-new conference series co-sponsored by FAES: **the IIG-FAES Symposia**, that will be open to extramural participants as well as the NIH/FDA community.

The first symposium of this conference series will focus on **Barrier Immunity**, and is slated to take place in the Natcher Conference Center (Building 45) from **Wednesday, November 15 to Friday, Novermber 17.** Please mark your calendar!

Formats include main talk sessions, poster sessions and workshops. More details on the symposia will be announced later by the IIG committee, please stay tuned!

We are looking forward to seeing everyone then!

Natcher Conference Center (Building 45), National Institutes of Health (NIH)



"Cell Defense"
This image was generated with the assistance of AI.

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Immunology Interest Group

SPOTLIGHT

Dr. Daniels is a Principal Investigator in the Division of Viral Products, Office of Vaccines Research and Review in CBER FDA.

To learn more about his work visit:
https://www.fda.gov/vaccines-blood-biologics/biologics-research-projects/influenza-neuraminidase-antigenicity-and-efficacy-vaccines

Robert Daniels, Ph.D.

Tell us about your science.

The long-term objectives of my lab are to increase efficacy of influenza vaccines that have primarily been developed to optimize immune responses to the influenza surface antigen hemagglutinin (HA). To reach this goal we are pursuing research centered around modifying new and existing vaccines to elicit protective antibody responses against additional influenza antigens (Ag). Currently, our major focus is on developing approaches to elicit protective antibody responses against the less abundant influenza surface Ag neuraminidase (NA) that are compatible with existing procedures for annual vaccine production and not dose restrictive. A key complementary component of this work is to determine the antigenic regions on circulating NA Ag that are protective so that the vaccine strain selection evaluation can begin to include the NA Ag.

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

I have always been curious. Ironically my first introduction to virology and immunology was English class where the teacher dropped the book entitled The Hot Zone by Richard Preston on my desk and said I think you might like it. I remember reading it in a matter of days, followed by the history of the Black plague and the fortuitous identification of smallpox vaccines that was based on a simple observation in milkmaids by Edward Jenner. This period really piqued my interest in pathogens that I still hold today.

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

I did not take a traditional academic path to becoming a PI and this decision presented many challenges which included trying to enter the influenza field without being classically trained by a well-known influenza lab. One of my first colleagues was instrumental in guiding me through some of these early more trying times by reminding me to focus on what you control, identify the questions that you are stimulated by and uniquely trained to investigate and to have fun. This philosophy helped to shape the way I decide the scientific direction of my lab today.

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

Combination therapy is a very common approach today for many drug-based therapies including antivirals. However, it was only introduced in the 1960s and we have not begun to scratch the surface of combination biologics. I believe in the next decade tthis approach will become clear should significantly improve the health and outcomes of patients.

What do you value most about the NIH-FDA Immunology community?

Coming to the Division of Viral Products has been eye-opening in terms of what constitutes a viable vaccine and how they are assessed. IIG has been especially helpful for learning about different types of immune responses and how these relate to vaccines. This has enhanced our research and ability to more properly assess nonclinical and clinical data.

How do you spend your free time?

Outdoors with my wife, son, daughter, and our cocker spaniel Mozart.

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SPOTLIGHT

Dr. Dang is a Principal Investigator in the Laboratory of Host Immunity and Microbiome of NIAID. To learn more about his work visit:
https://www.niaid.nih.gov/research/eric-van-dang-phd


Eric V Dang, Ph.D.

Tell us about your science.
My group is interested in understanding the mechanisms underlying protective versus pathological immune responses to fungi, and reciprocally, how fungi evade immunity to cause infection. My background is a hybrid of molecular/cellular immunology and fungal genetics so I try to operate at both sides of the coin, although immunology is my first love. We're doing a lot of work trying to understand host- and microbe-derived factors that influence macrophage activation states in the lung, and how these states influence infection outcomes. We're also tackling some questions related to fungal sensing mechanisms utilized by innate immune cells during infection. When I started my postdoc in a fungal genetics lab, I was struck by how much more advanced yeast genetics is compared to mammalian genetics, and how this technical advantage influences the types of questions that yeast geneticists ask. We're developing a number of systems to apply yeast forward genetics thinking to macrophages to get answers to fundamental questions in anti-fungal innate immunity.

What event(s) lead to your career in science and interest in immunology?
Certainly, one of the major factors that influenced my decision to pursue a career in science was my father, who is a cancer researcher. My specific interest in immunology came in part from luck; when I was an undergraduate at Johns Hopkins I wanted to start working in a lab and emailed a number of PIs to inquire about positions. I was fortunate to get a response from Dr. Drew Pardoll, who trained here at the NIH back in the day, and he let me dive into some projects on T cell biology. I was pretty much hooked from there.

How has a mentor or colleague substantially influenced your career trajectory?
Far and away the greatest influence on my career trajectory has been my PhD advisor Jason Cyster when I was a graduate student at UCSF. Jason really taught me what it means to be a scientist, how to focus in on a question, and to strive to become a world expert on whatever it is that you're working on. Without his support I wouldn't be where I am.

In what area(s) do you expect significant research/medical advances in the next 5-10 years?
In most instances, the most significant advances are the things you can't predict! But that being said, we're in a very exciting time in science. I think we're just scratching the surface of understanding how peripheral tissue and mucosa-specific niches control immune cell fate and function. There's also a lot to learn about trans-kingdom microbial interactions during infection, since much of our understanding of immune responses is derived from mono-infection systems. Broadly speaking, I suspect the most significant advances will emerge from cross-disciplinary thinking that breaks the trend of increasing sub-specialization.

What do you value most about the NIH-FDA Immunology community?
Having just around on campus this past September, I've been struck by how warm and collegial the environment is here at the NIH. The number of joint lab meetings/working groups that bring together multiple labs across different disciplines is a very unique feature here that makes collaborations easy and fun.

How do you spend your free time?
It is in short supply these days, but mostly cooking at home and playing with my German Shepherd. My favorite recreational activities are hiking and backpacking, though I still need to find the right spots here on the East Coast after spending a decade in California. I like to spend my free time with my family. I enjoy nature very much. Black Hill Regional Park in Boyds, MD is my favorite go to place for a walk on a nice sunny day.

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Bench-to-Bedside in Action

Translating immunology to transform clinical care

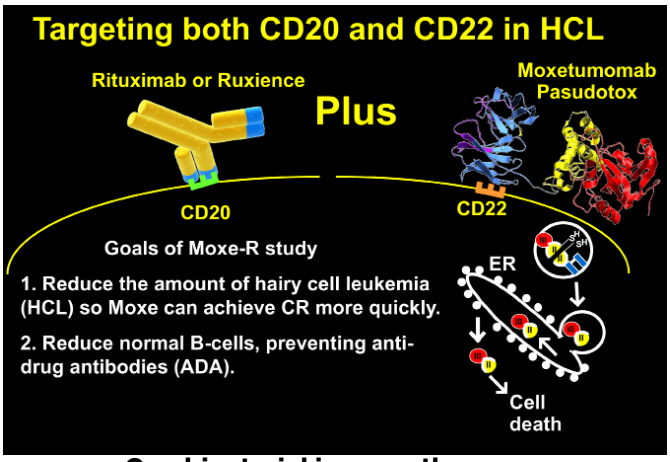
Harnessing fundamental knowledge to advance our understanding of disease and develop novel treatment strategies is a major mission of the NIH. Each month we highlight interesting clinical trials taking place at the NIH Clinical Center that are doing just that.

Lumoxiti (TM) and either Rituximab (Rituxan (R)) or Ruxience for Relapsed Hairy Cell Leukemia
PI: Robert J. Kreitman, M.D. – Chief, Clinical Immunotherapy Section, Laboratory of Molecular Biology, NCI, DIR.

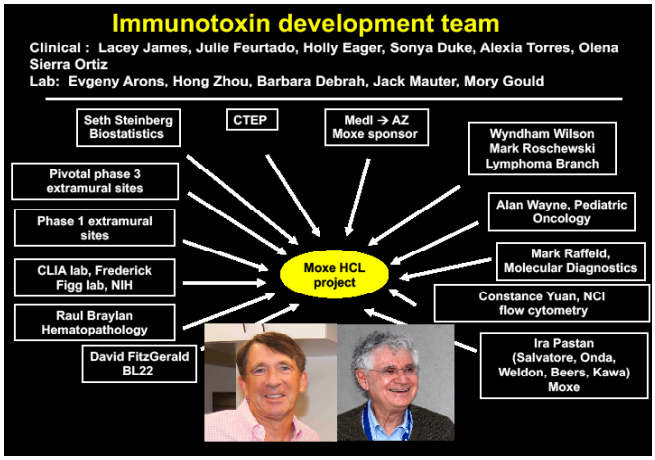
Background: Moxetumomab Pasudotox (Moxe) is a recombinant CD22 immunotoxin containing the variable domains of CD22 Mab and truncated Pseudomonas exotoxin. After binding to CD22 on the cell surface, Moxe is internalized and proteolytically cleaved within domain II, and the carboxyl terminus containing the enzymatic Domain III traffics to the endoplasmic reticulum (ER), translocates from the ER to the cytosol, and ADP-ribosylates elongation factor 2 (EF-2), resulting in apoptotic cell death. Hairy cell leukemia (HCL) is a rare mature B cell leukemia. Moxe was FDA-approved as a single agent for relapsed/refractory HCL, which highly expresses CD22, with a complete response (CR) rate of 41% in phase 3 testing, 34% CR without minimal residual disease (MRD).

Hypothesis: In this trial, Moxe is combined with an anti-CD22 Mab rituximab or Ruxience to evaluate whether this combination would increase the CR and MRD-free CR rates.

What we hope to learn: The proposed mechanism of adding Moxe to a Anti-CD20 monoclonal antibody would be to combine the reduction in the number of HCL cells using Moxe in parallel with reducing normal B-cell levels (Rituximab or Ruxience) to prevent anti-drug antibody (ADA) production. As published at the American Society of Clinical Oncology (ASCO) meeting, 2021, preliminary data in 9 patients, 78% achieved, CR, all of them MRD-free. We believe this regimen can be adapted in the future to achieve MRD-free CRs in newly diagnosed HCL, and to target MRD in patients with CD22+ lymphomas.



Combinatorial immunotherapy strategy to treat hairy cell leukemia.
The combined approach is schematized above. CR: complete remission, ADA: anti-drug antibodies



Moxe HCL Project Developmental Team

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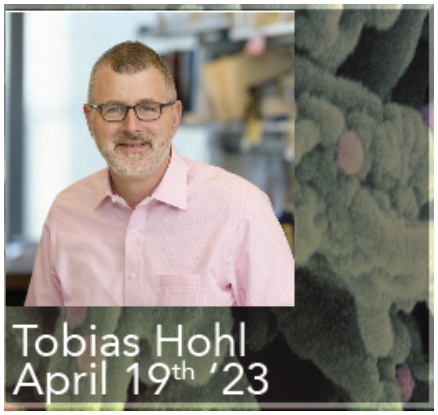
SEMINAR SERIES

Upcoming seminars



Missed a seminar?

Catch up on prior talks at...

https://www.niaid.nih.gov/research/immunology-seminars

FDA: http://web.microsoftstream.com/channel/5c371a75-2d56-45d3-9f86-7bacc3015066

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

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https://www.niaid.nih.gov/research/immunology-interest-group

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