NIH-FDA IIG

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

NEWSLETTER

JANUARY 2023

PUBLICATIONS

Enhanced virulence and waning vaccine-elicited antibodies account for breakthrough infections caused by SARS-CoV-2 delta and beyond

Kwon HJ, Kosikova M, Tang W, Ortega-Rodriguez U, Radvak P, Xiang R, Mercer KE, Muskhelishvili L, Davis K, Ward JM, Kosik I, Holly J, Kang I, Yewdell JW, Plant EP, Chen WH, Shriver MC, Barnes RS, Pasetti MF, Zhou B, Wentworth DE, Xie H

iScience. 2022 Dec 22; 25(12) 105507

DOI: 10.1016/j.isci.2022.105507, PMID: 36373096, PMCID: PMC9635945

This work was to investigate SARS-CoV-2 breakthrough infections in a mouse passive transfer and challenge model. The results reveal that enhanced virulence (e.g. Delta and Kappa variants), greater immune evasion (e.g. Delta and Omicron subvariants) and waning of vaccine-elicited neutralizing antibodies account for breakthrough infections during the Delta dominant wave and beyond.

Double knockin mice show NF-B trajectories in immune signaling and aging

Rahman SMT, Aqdas M, Martin EW, Tomassoni Ardori F, Songkiatisak P, Oh KS, Uderhardt S, Yun S, Claybourne QC, McDevitt RA, Greco V, Germain RN, Tessarollo L, Sung MH

Cell Rep. 2022 Nov 22; 41(8) 111682

DOI: 10.1016/j.celrep.2022.111682, PMID: 36417863, PMCID: PMC9764224

We present fluorescent knock-in mice that track one or both of the canonical subunits of NF- B. The mice enable diverse applications from single-molecule analyses to in situ identification of active inflammatory cells.

Human Dectin-1 deficiency impairs macrophage-mediated defense against phaeohyphomycosis

Drummond RA, Desai JV, Hsu AP, Oikonomou V, Vinh DC, Acklin JA, Abers MS, Walkiewicz MA, Anzick SL, Swamydas M, Vautier S, Natarajan M, Oler AJ, Yamanaka D, Mayer-Barber KD, Iwakura Y, Bianchi D, Driscoll B, Hauck K, Kline A, Viall NS, Zerbe CS, Ferré EM, Schmitt MM, DiMaggio T, Pittaluga S, Butman JA, Zelazny AM, Shea YR, Arias CA, Ashbaugh C, Mahmood M, Temesgen Z, Theofiles AG, Nigo M, Moudgal V, Bloch KC, Kelly SG, Whitworth MS, Rao G, Whitener CJ, Mafi N, Gea-Banacloche J, Kenyon LC, Miller WR, Boggian K, Gilbert A, Sincock M, Freeman AF, Bennett JE, Hasbun R, Mikelis CM, Kwon-Chung KJ, Belkaid Y, Brown GD, Lim JK, Kuhns DB, Holland SM, Lionakis MS

J Clin Invest. 2022 Nov 15; 132(22)

DOI: 10.1172/JCI159348, PMID: 36377664, PMCID: PMC9663159

Dectin-1 is a receptor important for innate recognition of pathogenic fungi. In this work, we find that loss of this single receptor in mice and humans predisposes to the fungal infection phaeohyphomycosis by disrupting macrophage-mediated killing of fungi via IL-1b and TNFa.

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NF-kB dynamics in the language of immune cells

Aqdas M, Sung MH
Trends Immunol. 2023 Jan; 44(1) 32-43
DOI: 10.1016/j.it.2022.11.005, PMID: 36473794, PMCID: PMC9811507

Recent techniques enable capturing endogenous NF-kB dynamics in primary immune cells and live tissues and should be used to carefully evaluate how NF- kB conveys biological information. Such signaling dynamics may be important for a widely activated transcription factor in promoting accurate cell decision-making in immune cell development and function.

Antigen-presenting T cells provide critical B7 co-stimulation for thymic iNKT cell development via CD28-dependent trogocytosis

Watanabe M, Celli S, Alkhaleel FA, Hodes RJ
Cell Rep. 2022 Nov 29; 41(9) 111731
DOI: 10.1016/j.celrep.2022.111731, PMID: 36450247, PMCID: PMC9805342

We show that CD28 expression on CD1d-expressing antigen-presenting T cells is required for thymic iNKT cell development. Mechanistically, antigen-presenting T cells provide B7 co-stimulation through an unconventional mechanism, acquiring B7 molecules via CD28-dependent trogocytosis from B7-expressing thymic epithelial cells, dendritic cells, and B cells and providing critical B7 co-stimulation to developing iNKT cells. Thus, the present study demonstrates a mechanism of B7 co-stimulation in thymic T cell development by antigen-presenting T cells.

An Interleukin-15 Superagonist Enables Antitumor Efficacy of Natural Killer Cells Against All Molecular Variants of SCLC

Fousek K, Horn LA, Qin H, Dahut M, Iida M, Yacubovich D, Hamilton DH, Thomas A, Schlom J, Palena C.
J Thorac Oncol. 2022 Nov 21:S1556-0864(22)01910-4
DOI: 10.1016/j.jtho.2022.11.008, PMID: 36410696

Novel and more effective therapeutic approaches for the treatment of SCLC, an aggressive type of lung cancer with a 5-year overall survival rate of only 6%, are urgently needed. In an attempt to devise a more effective immunotherapeutic regimen for SCLC, this study investigated an alternative approach using the clinical-stage interleukin-15 superagonist, N-803. Our findings suggest that N-803 may provide clinical benefit to most patients with SCLC across all molecular variants, including those with immunologically cold tumors lacking MHC-class I expression.

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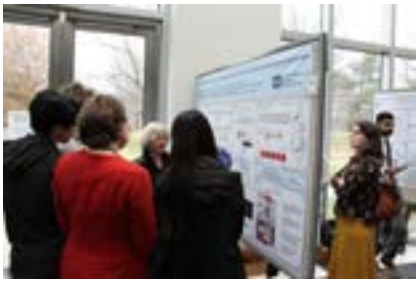
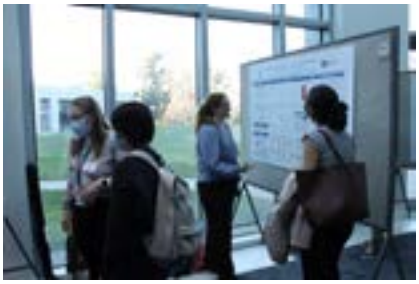
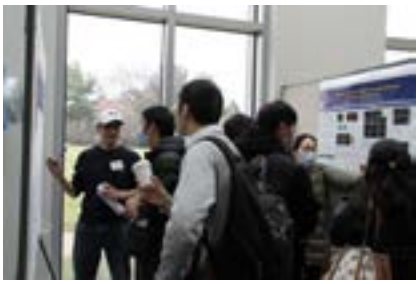
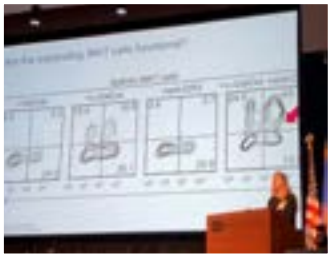
2022 IIG Workshop

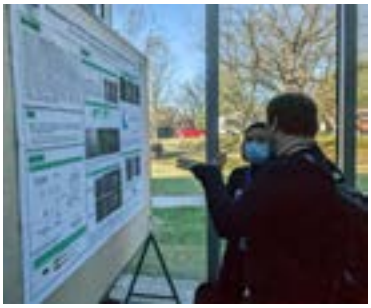
The 2022 hybrid IIG Workshop physically brought the community together for the first time since the pandemic started. The stimulating presentations, and more importantly – people behind the science, brightened the workshop. Here is a glimpse of the intellectual, heart-warming, and sometimes whimsical moments at the workshop.

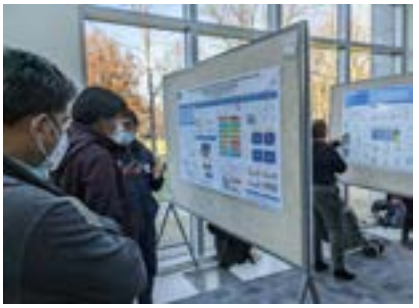












Immunology Interest Group

SPOTLIGHT

Dr. Mayer is an Earl Stadtman Tenure-Track Investigator and Chief of the Experimental Immunology Branch in the National Cancer Institute.

To learn more about his work visit:
https://irp.nih.gov/pi/christian-mayer

Christian Mayer, Ph.D.

Tell us about your science.

My lab is interested in mechanisms of immune regulation. In that regard, we currently focus on investigating the role of programmed cell death during immune cell development, activation, differentiation, and function. We have developed a mouse model to indicate the apoptosis event in vivo. This important tool aiding our research was named "INDIA" (Indicator of Apoptosis). These studies serve to increase our fundamental understanding of immune responses and of how defective immune regulation might contribute to diseases. The long-term goals are to identify new therapeutic strategies to (1) inhibit off-target immune responses to self- and harmless antigens, (2) enhance desired immune responses against tumors and pathogens.

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

One key event was being gifted a chemistry kit as a teenager. I gradually turned one room at our house into a "lab" and enjoyed accumulating new equipment and chemicals to do experiments. Some of the experiments left permanent marks in the "lab". I would say my interest in immunology was also triggered by knowing people with autoimmune diseases and by the desire to better understand what causes them and how they could be more specifically treated.

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

Both my PhD- and postdoctoral mentors played important roles through their guidance and continued support. It is generally a good idea to choose these carefully and, if possible, get to know them in advance. For example, I first did my Master's thesis for several months before deciding to continue with my PhD in the same lab. My PhD mentor also suggested to invite PIs of potential Postdoc labs to our institute as seminar/symposium speakers to get to know them before visiting their lab for interviews.

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

I think more advances will be made in the treatment/prevention of autoimmune and infectious diseases as well as in immunotherapy of various cancers. The successful mRNA delivery platform as well as continued basic and clinical research in immunology all seem exciting for these avenues.

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

The diversity and expertise in so many different areas of immunology.

How do you spend your free time?

Growing, maintaining, and attempting to clone orchids and other plants, listening to music, cooking, exercising.

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Immunology Interest Group
SPOTLIGHT

Dr. Mandal is an investigator in the Tumor Vaccines and Biotechnology Branch in the Office of Tissues and Advanced Therapies of CBER. To learn more about his work visit: https://www.fda.gov/vaccines-blood-biologics/biologics-research-projects/genome-editing-and-advanced-manufacturing-hematopoietic-stem-cell-based-therapeutics

Pankaj Mandal, Ph.D.

Tell us about your science.
Our laboratory studies advanced manufacturing of hematopoietic stem cell-based therapeutics. Our goal is to define the optimal condition for cost-effective, large-scale manufacturing of genome-edited HSC and to develop methods to improve manufacturing of HSCs and HSC-derived therapeutics.

What event(s) lead to your career in science and interest in immunology?
Since my school days, I have been interested in studying biological science. After finishing my bachelor's degree in Veterinary Sciences, I enrolled in a master program in veterinary immunology and carried out a research project characterizing Rous Sarcoma virus-induced tumor antigens. That exposure to research during my master's degree converted a veterinarian into a scientist.

How has a mentor or colleague substantially influenced your career trajectory?
I consider my-self fortunate to have exceptionally talented colleagues, teachers, and mentors throughout my career who influenced my career trajectory in numerous ways. They are my source of inspiration. My postdoc mentor Dr. Derrick Rossi provided me with a research environment and independence to explore and grow as a scientist. I thoroughly enjoyed my time in his lab, working on some of the cutting-edge technologies such as modified mRNA, iPS reprogramming, and CRISPR genome editing in human cell types etc.

In what area(s) do you expect significant research/medical advances in the next 5-10 years?
I think in the next 5-10 years, we will witness implementation of genetic engineering for developing novel therapeutics. We will see increasing use of AI/machine learning in drug development. Personalized medicine is another area where significant advancement will be made in the next 5-10 years.

What do you value most about the NIH-FDA Immunology community?
The NIH-FDA IIG is a collaborative platform to conduct and share cutting-edge research. I like the NIH-FDA IIG seminar series and the workshop.

How do you spend your free time?
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

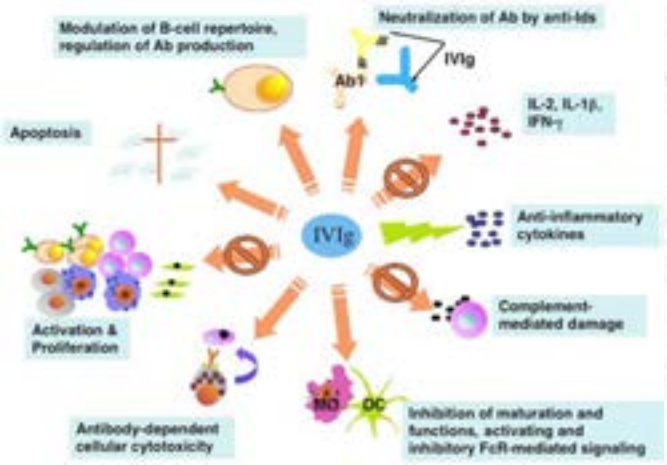
Harnessing fundamental knowledge to advance our understanding of disease and develop novel treatment strategies is a major mission of the NIH. Each month we highlight interesting clinical trials taking place at the NIH Clinical Center that are doing just that.

Immunotherapy for Neurological Post-Acute Sequela of SARS-CoV-2 (IN-PASC)

PI: Avindra Nath, M.D. – Clinical Director and Chief, Section of Infections in the Nervous System, NINDS, DIR.

Background: The Post-Acute Sequelae of SARS-CoV-2 infection (PASC), often referred to as "Long COVID", encompasses a constellation of symptoms that last for weeks to months after resolution of the acute infection. In some cases, it may emerge after a hiatus of a few days or weeks following a mild infection. Exercise intolerance, dyspnea, cognitive and mental disorders, pain, dysautonomia, smell and taste dysfunction, and gastrointestinal issues are the most common symptoms. The heterogeneity in clinical features suggests multiple underlying pathophysiological processes. In a subset of individuals, persistent immune activation and/or retained SARS-CoV-2 antigen have been implicated. This is supported by preliminary data in our cohort of PASC patients showing immune dysregulation with reduced effector memory T-cells, increased programmed cell death protein 1 (PD-1) on monocytes and increased frequency of activated B-cells and NK cells in both blood and CSF compared to healthy controls.

Hypothesis: Immunotherapy with intravenous immunoglobulin (IVIg), which has broad effects on the immune system, known efficacy in neurologic and rheumatic diseases, and anti-viral activity stands out as an immediately available intervention for PASC.



Schematic of potential mechanisms of action of IVIg to blunt immune activation.
Figure from Negi VS et al. J. Clin. Immunology
https://pubmed.ncbi.nlm.nih.gov/17351760/

Study Design: NCT05350774 is a double-blind, placebo controlled cross-over study designed to determine if a 5-day course of IVIg treatment leads to a clinically meaningful improvement in PASC symptoms. Improvement will be measured with patient reported outcome tools, blood-derived immunological markers, and autonomic tests. Planned immunological markers include flow cytometry to investigate T-cell, B-cell, and NK cell subtypes as well as markers of activation/exhaustion including PD-1, TIGIT, CD244, and CD266) and multiplex cytokine assays (Mesoscale V-plex 77-analyte assay, Luminex MagPix) with the intent of interrogating the IL-17, IL-10, interferon signaling pathways, and markers of innate immune activation. Other measures include neuronal injury makers (e.g. tau, ptau, and neurofilament light chain), catecholamines, and renin-angiotensin-aldosterone markers. Viral antigen will also be monitored in various tissue compartments.

What we hope to learn: The clinical value of IVIg as a treatment for the neurologic complications of PASC and what biological markers may serve as either predictors of treatment responsiveness or indicators of a successful response.

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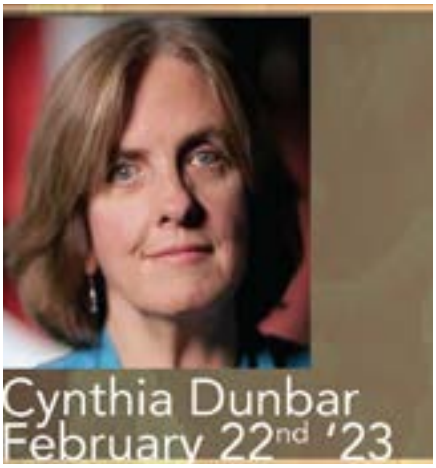
Immunology Interest Group
SEMINAR SERIES

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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Immunology Interest Group

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