# NIH-FDA IIG

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

# NEWSLETTER

## APRIL 2022

## PUBLICATIONS

### Deconvolving Clinically Relevant Cellular Immune Cross-talk from Bulk Gene Expression Using CODEFACS and LIRICS Stratifies Patients with Melanoma to Anti-PD-1 Therapy

Wang K, Patkar S, Lee JS, Gertz EM, Robinson W, Schischlik F, Crawford DR, Schaffer AA, Ruppin E
Cancer Discovery 12:1088--1105, 2022.
DOI: 10.1158/2159-8290.CD-21-0887, PMID: 34983745
*We developed a new computational method called CODEFACS (COnfident DEconvolution For All Cell Subsets) that takes bulk RNA expression data for a cohort of samples and signatures for different cell types and provides as output an estimate of the expression of each gene in each cell type in each sample. We also developed a curated database and method called LIRICS (Ligand Receptor Interactions for all Cell Subsets) to identify cell-type specific ligand-receptor interactions predictive of responses to immunotherapy based on CODEFACS-deconvolved gene expression data and prior immunological knowledge.*

### Mucus sialylation determines intestinal host-commensal homeostasis

Yao Y, Kim G, Shafer S, Chen Z, Kubo S, Ji Y, Luo J, Yang W, Perner SP, Kanellopoulou C, Park AY, Jiang P, Li J, Baris S, Aydiner EK, Ertem D, Mulder DJ, Warner N, Griffiths AM, Topf-Olivestone C, Kori M, Werner L, Ouahed J, Field M, Liu C, Schwarz B, Bosio CM, Ganesan S, Song J, Urlaub H, Oellerich T, Malaker SA, Zheng L, Bertozzi CR, Zhang Y, Matthews H, Montgomery W, Shih HY, Jiang J, Jones M, Baras A, Shuldiner A, Gonzaga-Jauregui C, Snapper SB, Muise AM, Shouval DS, Ozen A, Pan KT, Wu C, Lenardo MJ
Cell. 2022 Mar 31; 185(7) 1172-1188.e28
DOI: 10.1016/j.cell.2022.02.013, PMID: 35303419
*This study identifies the role of sialylation in protecting intestinal mucus integrity from bacterial degradation, establishing host-microbial symbiosis and gut homeostatic environment.*

### Mild SARS-CoV-2 infection in rhesus macaques is associated with viral control prior to antigen-specific T cell responses in tissues

Nelson CE, Namasivayam S, Foreman TW, Kauffman KD, Sakai S, Dorosky DE, Lora NE, NIAID/DIR Tuberculosis Imaging Program 3 ǂ, Brooks K, Potter EL, Garza NL, Lafont BAP, Johnson RF, Roederer M, Sher A, Weiskopf D, Sette A, de Wit E, Hickman HD, Brenchley JM, Via LE, Barber DL, Abdi A, Dayao EK, Fleegle JD, Gomez F, Piazza MK, Repoli KM, Sloan BY, Butler AL, Walker AM, Weiner DM, Woodcock MJ, Vatthauer A
Sci Immunol. 2022 Mar 10; eabo0535
DOI: 10.1126/sciimmunol.abo0535, PMID: 35271298
*SARS-CoV-2 infection of macaques leads to mild lung inflammation and early type I IFN activated myeloid cell responses in the blood and airways, both of which resolve prior to the expansion of antigen-specific T cells responses. In this model, SARS-CoV-2 antigen specific T cells are preferentially localized in the lung parenchyma and airways and are notably absent from upper airway mucosal tissues including nasal turbinates, tonsils, and salivary glands.*

### Dntt expression reveals developmental hierarchy and lineage specification of hematopoietic progenitors

Klein F, Roux J, Cvijetic G, Rodrigues PF, von Muenchow L, Lubin R, Pelczar P, Yona S, Tsapogas P, Tussiwand R
Nat Immunol. 2022 Apr;23(4):505-517.
DOI: 10.1038/s41590-022-01167-5, PMID: 35354960
*We have dissected the transcriptional landscape of early Hematopoietic cells, identifying a new subset of multipotent progenitors downstream HSCs. Further we show that expression of TdT or other lineage specific transcripts is uncoupled form lineage commitment. Specification towards each hematopoietic branch occurs upon downregulation of the surface receptor ESAM.*

**Continued>>**

## The transcription factor LRF promotes integrin β7 expression by and gut homing of CD8αα+ intraepithelial lymphocyte precursors

Nie J, Carpenter AC, Chopp LB, Chen T, Balmaceno-Criss M, Ciucci T, Xiao Q, Kelly MC, McGavern DB, Belkaid Y, Bosselut R

Nat Immunol. 2022 Apr;23(4):594-604.

DOI: 10.1038/s41590-022-01161-x, PMID: 35354951

*We show that mouse thymocytes deficient for the transcription factor leukemia/lymphoma-related factor (LRF) failed to generate TCRαβ+CD8αα+ intraepithelial lymphocytes (IELs) and their CD8β-expressing counterparts, despite giving rise to thymus and spleen CD8αβ+ T cells. LRF-deficient IELps failed to migrate to the intestine and to protect against T cell-induced colitis, and had impaired expression of the gut-homing integrin α4β7.Our study identifies LRF as an essential transcriptional regulator of IELp maturation in the thymus and subsequent migration to the intestinal epithelium.*

## CRISPR Screen to Identify Factors that Render Tumor Cells Sensitive or Resistant to Killing by NK Cells

Zhuang X, Long EO.

Methods Mol Biol. 2022;2463:269-288.

DOI: 10.1007/978-1-0716-2160-8_19, PMID: 35344181

*We provide a protocol for a genome-wide CRISPR screen in tumor cells to identify factors that regulate their sensitivity to primary human NK cells.*

## Structure-based design of stabilized recombinant influenza neuraminidase tetramers

Ellis D, Lederhofer J, Acton OJ, Tsybovsky Y, Kephart S, Yap C, Gillespie RA, Creanga A, Olshefsky A, Stephens T, Pettie D, Murphy M, Sydeman C, Ahlrichs M, Chan S, Borst AJ, Park YJ, Lee KK, Graham BS, Veesler D, King NP, Kanekiyo M

Nat Commun. 2022 Apr 5;13(1):1825.

DOI: 10.1038/s41467-022-29416-z., PMID: 35383176

*Influenza virus neuraminidase (NA) is a drug target and a potential vaccine antigen. Here, the authors provide a detailed analysis of the conformational stability of NA, and show how expression and stability of recombinant NA antigens can be strengthened through structure-based design.*

## Dynamic immunodominance hierarchy of neutralizing antibody responses to evolving GII.4 noroviruses

Tohma K, Ford-Siltz LA, Kendra JA, Parra GI

Cell Rep. 2022 Apr 12;39(2):110689.

DOI: 10.1016/j.celrep.2022.110689, PMID: 35417705

*We comprehensively characterized all variable antigenic sites involved in norovirus neutralization and found remarkable differences in the mAb-binding profiles for two distantly related virus variants. Time-ordered mutant viruses confirmed a progressive change of antibody immunodominance that might facilitate antibody escape. .*

## Differential regulation of transcription factor T-bet induction during NK cell development and T helper-1 cell differentiation

Fang D, Cui K, Cao Y, Zheng M, Kawabe T, Hu G, Khillan JS, Li D, Zhong C, Jankovic D, Sher A, Zhao K, Zhu J

Immunity, 2022 Apr 12;55(4):639-655.e7

DOI: 10.1016/j.immuni.2022.03.005, PMID: 35381213

*This study shows that type 1 innate and adaptive lymphocytes utilize distinct cis-regulatory elements at the Tbx21 locus for T-bet induction during their development, differentiation, and activation.*



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# Immunology Interest Group

# SPOTLIGHT

**Dr. Ye is an investigator in the Division of Cellular and Gene Therapies, Gene Transfer and Immunogenicity Branch, FDA. To learn more about his work visit: [https://www.fda.gov/vaccines-blood-biologics/biologics-research-projects/evaluation-therapeutic-approaches-based-genome-editing-and-stem-cell-technologies](https://www.fda.gov/vaccines-blood-biologics/biologics-research-projects/evaluation-therapeutic-approaches-based-genome-editing-and-stem-cell-technologies)**

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

Our laboratory studies cell fate determination of human pluripotent stem cells. We are particularly interested in genetic and environmental factors that are important for hematopoietic and lymphoid differentiation from iPSCs. We use cell culture, genetic engineering, and animal transplantation to characterize different cell types generated through in vitro differentiation. As genetic modifications are increasingly used to enhance cell-based immunotherapies, we also study efficacy and specificity of these technologies such as CRISPR-based genome or epigenome editors.

Zhaohui Ye, Ph.D.

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

It's difficult to pinpoint specific events that led to a science career. I have been interested in science since a very young age when I was told that being a scientist would be the best way to serve society. So I think it is more about a lack of events that could have lured me away from science. My initial interest in immunology developed during my senior year in college, when I did a year-long thesis research on how tobacco plants fights off pathogens (not the type of immunology that most folks here are familiar with). My later decision to switch to human biology study wasn't too difficult once I came to the realization that it would be more fulfilling improving human health than growing robust tobaccos.

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

My PhD advisor Dr. Linzhao Cheng has been a great mentor for many years. Besides opening up my eyes to the word of stem cell research, he taught me the basic principles of choosing and planning a research project. His passion for cutting edge technologies also inspired many trained or worked with him.

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

Regenerative medicine in general. Cancer immunotherapies will continue to have breakthroughs (e.g., against solid tumors). New vaccines.

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

Training opportunities; great selection of seminar speakers.

***How do you spend your free time?***

Free time is hard to come by these days, but if there is any, I do my best to keep the plants (no tobaccos) in our yard alive and thrive, and go to parks with kids.



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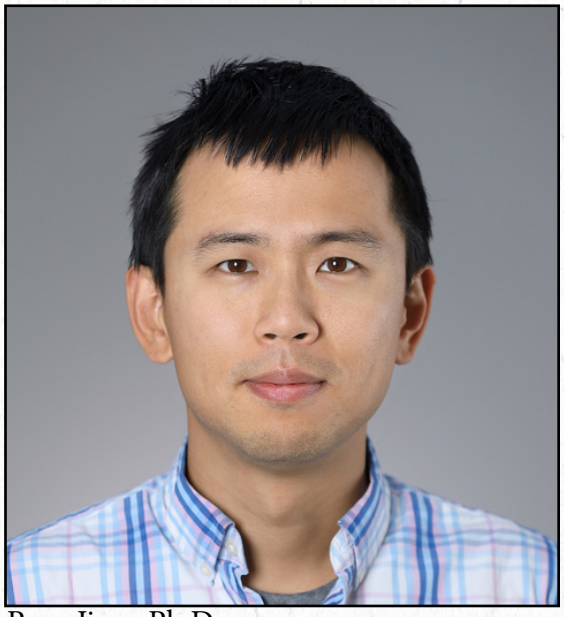
# Immunology Interest Group

# SPOTLIGHT

**Dr. Jiang is an Stadtman Tenure-track Investigator in the Center for Cancer Research, National Cancer Institute and leads the Cancer Data Science Lab. To learn more about his work visit: https://ccr.cancer.gov/staff-directory/peng-jiang#staff-profile**

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

My research focuses on developing data integration frameworks to find biomarkers of cancer immunotherapy response and regulators of tumor immune evasion. Most people know me because of the TIDE web app for immuno-oncology research (http://tide.dfci.harvard.edu). As the biology field is generating massive amounts of data to study diverse immunological processes, my team and I are developing frameworks and models so the whole community can easily leverage the vast amount of public data in their new studies. An example is the CytoSig framework for cytokine signaling research (https://cytosig.ccr.cancer.gov). My team also has a wet-lab component, which utilized data-driven models that we generated (https://resilience.ccr.cancer.gov) to identify therapeutic targets to enhance cellular immunotherapies in solid tumors.



Peng Jiang Ph.D.

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

During the 4th year of my postdoc training at Xiaole Liu Lab at Harvard, I started collaborating with Prof. Kai Wucherpfennig, which turned out to be a turning point in my career. Before this collaboration, I had never had any experience in immunology research. However, through interactions with Kai and his team, I was deeply amazed by immunology and realized that this field naturally provides many fascinating problems for computational biologists to study.

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

Related to the event above, Prof. Kai Wucherpfennig and Xiaole Liu substantially influenced my career trajectory. After collaborating with Kai, I decided to focus on developing computational approaches for immunology research.

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

I think cellular immunotherapies will have significant advances in the next ten years. Conventional anti-cancer drugs, either small molecules or antibodies, are static constructions. The drug will not change its strategy when it encounters complicated situations in a tumor microenvironment. However, cellular therapies are based on cellular systems armed with many bio-engineering modalities. Ideally, if we figure out how to train immune cells, therapeutic cells should become smart enough to deal with tumor cells that are constantly evolving and changing.

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

This community provides a platform for immunologists to exchange ideas, reagents, and essential information.

***How do you spend your free time?***

Outside my working hours, I spend time with my family, particularly my baby daughter.



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# NIBIB IRP Section on Immunoengineering Alumni selected for prestigious NSF Graduate Research Fellowship Program

Two NIBIB intramural trainees are recipients of 2022 National Science Foundation (NSF) Graduate Research Fellowship Program (GRFP) awards. Maria Karkanitsa and Tran Ngo, intramural trainees from NIBIB's Section on Immunoengineering, are among nearly 2,200 awardees nationally. Karkanitsa has entered a Ph.D. program in bioengineering at the University of California, San Diego. Ngo is a current Postbaccalaureate Intramural Research Training Fellow, who is in the process of matching with a graduate program in biomedical engineering.

From left, NSF GRFP Awardees: Kenneth Adusei, Maria Karkanitsa and Tran Ngo. NIBIB photo.

Kaitlyn Sadtler, Ph.D., NIBIB investigator and section chief, has mentored each of the awardees from her lab. "These fellows have been really fantastic and wonderful to work with in the lab. I have no doubt they will be—and are already—just brilliant scientists," Sadtler said. "We are very proud and excited for them."

Kenneth Adusei, an alumnus of the lab, was selected for the NSF Graduate Research Fellowship in 2021 and is currently a Ph.D. student in biomedical engineering at the Johns Hopkins University.

NSF's Graduate Research Fellowships recognize and support outstanding graduate students in NSF-supported STEM disciplines who are pursuing research-based master's and doctoral degrees at accredited U.S. institutions.

The five-year fellowship includes three years of financial support including an annual stipend of $34,000 and a cost of education allowance of $12,000 to the institution.

# NCI Fellow to Participate in SITC Women in Cancer Immunotherapy Network Leadership Institute Program

Dr. Enitome "Tome" Bafor, Ph.D., a post-doctoral fellow working to understand autoimmune reproductive failure in the Cancer Innovation Laboratory, NCI/CCR, led by Howard Young, Ph.D. has been selected to participate in the 2022 Society for Immunotherapy of Cancer (SITC) Women in Cancer Immunotherapy Network (WIN) Leadership Institute.

This program features presentations from experienced female leaders, panel discussions, and networking opportunities and aims to promote female scientists as emerging leaders in the field of cancer immunotherapy. Participants will develop and enhance leadership skills, as well as explore topics around diversity and inclusivity.


Enitome Bafor, Ph,D


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# Bench-to-Bedside in Action

## Translating immunology to transform clinical care

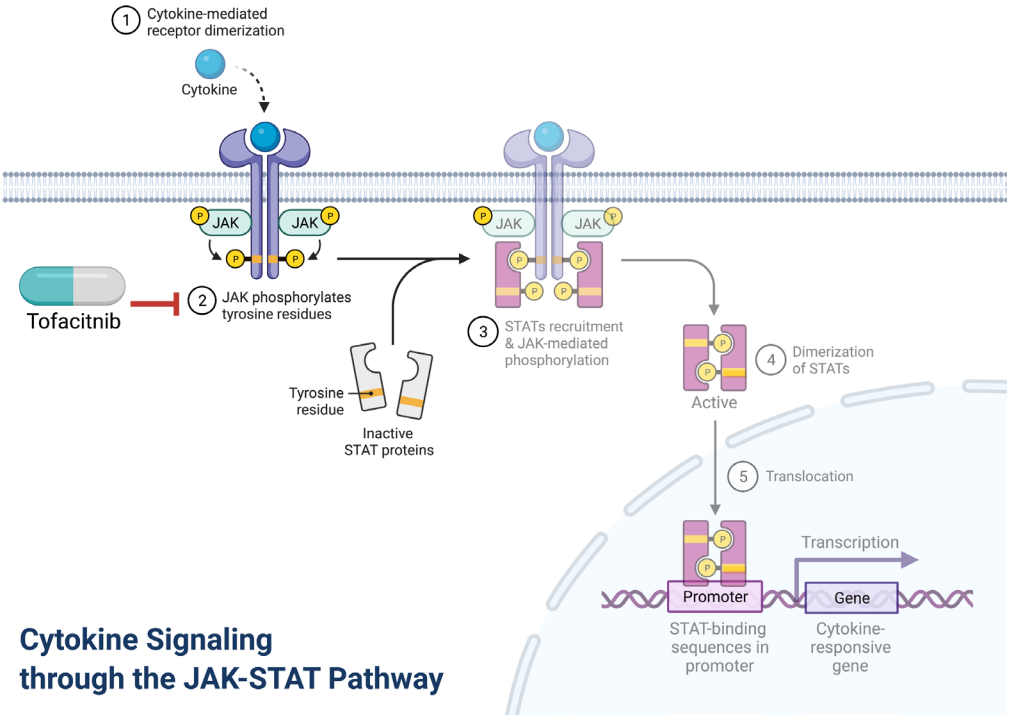
Harnessing fundamental knowledge to advance our understanding of disease and develop novel treatment strategies is a major mission of the NIH. Each month we highlight interesting clinical trials taking place at the NIH Clinical Center that are doing just that.

### Safety of Tofacitinib, an Oral Janus Kinase Inhibitor, in Primary Sjogren's Syndrome

PI: Blake M. Warner, D.D.S.
AI: Sarthak Gupta, M.D.

Sjögren's syndrome (SS) is a systemic autoimmune disease with heterogeneous clinical presentation. SS is manifested by chronic inflammatory lymphocytic infiltration of the exocrine glands. The current management of SS includes approaches to mitigate symptoms and immunosuppressants that are limited in their efficacy. Pathogenesis of SS involves the complex interaction of genetic, environmental, and hormonal factors. Activation of several biological pathways belonging to both innate and acquired immune systems have been reported. Many of the inflammatory cytokines implicated in SS pathogenesis, in particular Type I and II interferons (IFNs), IL-6, IL-7, IL-12, and IL-21, signal through JAK/STAT pathway (Figure).

Tofacitinib is an oral JAK inhibitor that is approved for treatment of various systemic autoimmune diseases. NIDCR, in collaboration with NIAMS and NEI, have launched a Phase Ib-IIa, randomized, double blinded, placebo controlled clinical trial of Tofacitinib, 5 mg twice daily, for treatment of individuals with mild to moderate SS disease. In this trial, Tofacitinib will be given to 20 SS patients, while 10 patients will receive placebo for a period of 6-months. The proposed clinical trial will yield preliminary data about the safety, and clinical and biologic efficacy of Tofacitinib in SS. In addition, this trial will help expand our understanding of the pathogenic cytokine milieu and resultant tissue dysfunction in SS.




**Cytokine Signaling through the JAK-STAT Pathway**

Made with Biorender

To learn more about this study, please visit: https://www.clinicaltrials.gov/ct2/show/NCT04496960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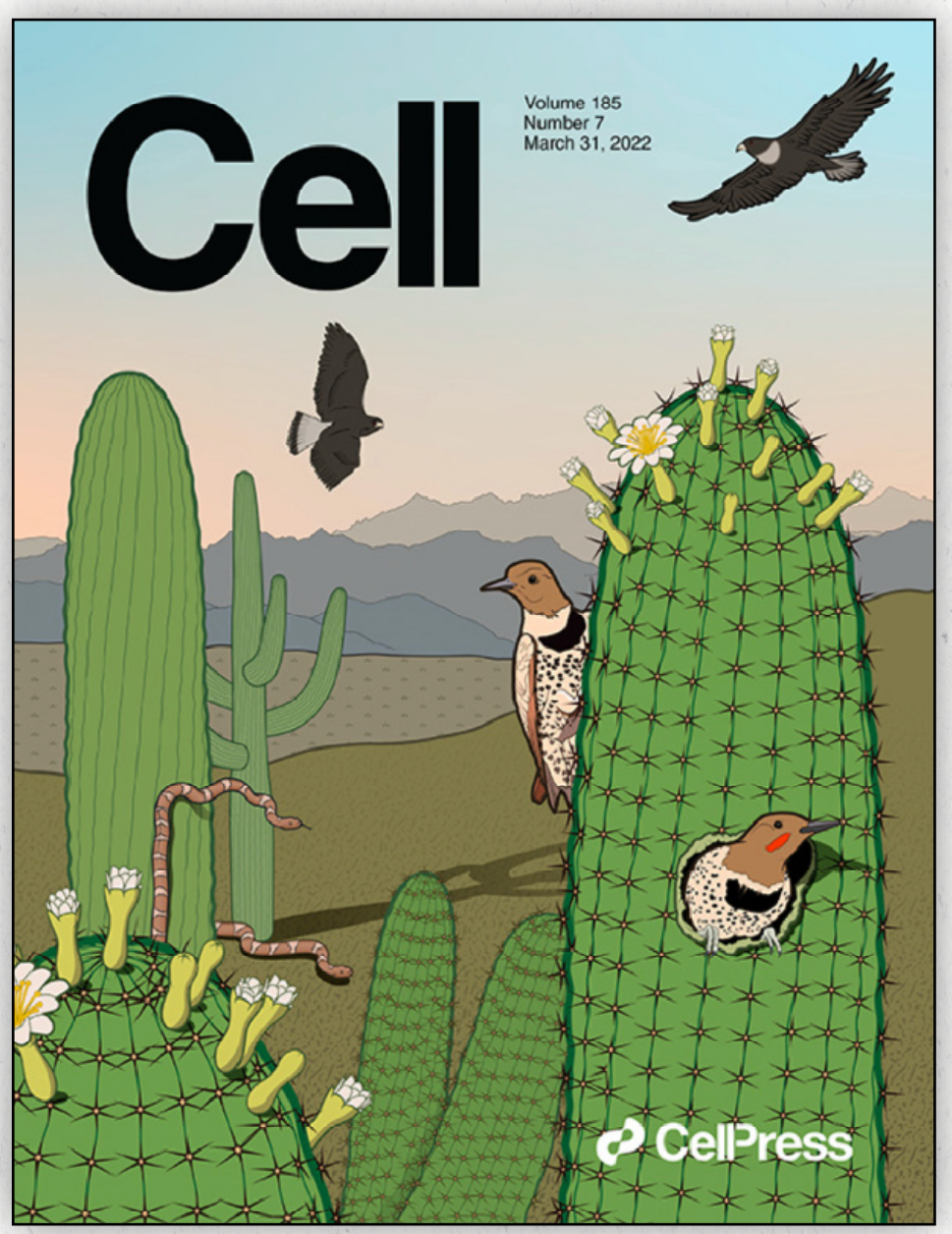
# The desert and the gut.




The March 31 cover of *Cell* illustrates that sialylated mucin proteins (saguaros with thorns) harbor symbiotic commensal bacteria (gilded flickers), protecting the intestinal tissue from pathogens (snakes and hawks). Loss of sialylation (saguaros without thorns) results in pathogenic bacteria invasion (snakes). Illustration concept by Chuan Wu (IIG) and Artwork by Alan Hoofring.

Sialylation is critical for intestinal mucus formation. Yao et al. show that a local sialyltransferase in the gut, ST-6GALNAC1 (ST6) determines mucin protein sialylation, protecting mucus barrier integrity from bacterial degradation. ST6-mediated mucus homeostasis in turn controls commensalism to establish intestinal host-microbial symbiosis. ST6 deficiency disrupts this mutualism, enhancing susceptibility to intestinal inflammation.

Mucus sialylation determines intestinal host-commensal homeostasis
Yao et al., Cell, 2022. PMID: 35303419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# 2022 IIG Workshop

## December 8–9, 2022 - Natcher Conference Center - BG 45

**Save the date for the 2022 Immunology Interest Group Workshop!**

**The NIH-FDA immunology community will convene Dec. 8 through 9th at the Natcher Conference Center (Building 45 on the NIH campus). The hybrid meeting platform will allow attendance to be in person with a virtual attendance option (at least for the plenary and oral sessions; options for virtual poster presentations are under investigation).**

**Stay tuned for future announcements.**

# *Introducing our Workshop Gurus*

**Ericka Pearce, Ph.D.**
**Bloomberg Distinguished Professor**
**Johns Hopkins University**

**Yasmine Belkaid, Ph.D.**
**Chief, Laboratory of Host Immunity and Microbiome**
**NIAID**

*Continued>>*

# Immunology Interest Group
# SEMINAR SERIES

## May 2022

May 4, 2022
**Florent Ginhoux**
Myeloid cell heterogeneity

May 18, 2022
**Peng Jiang**
Big Data Approaches to Study Intercellular Signaling in Cancer Immunology Resistance

May 25, 2022
**Garry Nolan**
Cancer rearranges the rules in tissue building blocks. A new class of targets for therapy?

## June 2022

June 1, 2022
**Joonsoo Kang**
Regulation of mucocutaneous inflammation and innate lymphocytes by cholesterol metabolites

June 8, 2022
**Akiko Iwasaki**
Immune response to SARS-CoV-2

June 15, 2022
**Gillian Griffiths****
Identifying novel genes that impact T cell effector function

June 22, 2022
**Vishva Dixit**
Why so many ways to die?

June 29, 2022
**Hans-Reimer Rodewald**
Deconvolution of hematopoiesis and immune responses by Polylox barcoding

# Missed a seminar?

## Catch up on all your 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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# Join the List Serve!
## Immunology Interest Group

Share with new colleagues and trainees
that join the lab:

Please visit the IIG website and (re)subscribe to the
IMMUNI-L NIH Listserv with your
NIH or FDA email address:

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

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