

# NIH-FDA IIG

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

## NEWSLETTER

FEBRUARY 2022

PUBLICATIONS

### **GCgx: transcriptome-wide exploration of the response to glucocorticoids**

Cao Q, Boo Irizarry Y, Yazhuk S, Tran T, Gadkari M, Franco LM. *J Mol Endocrinol.* 2021;68(2):B1-B4.

PMID: 34787097. PMCID: PMC8691098. DOI: 10.1530/JME-21-0107

*We introduce GCgx (<https://gcgx.niaid.nih.gov>), a web application that allows investigators to quickly visualize changes in transcript abundance in response to glucocorticoids in a variety of cells and species.*

### **Intestinal IL-33 promotes platelet activity for neutrophil recruitment during acute inflammation**

Chen Z, Luo J, Li J, Kim G, Stewart CA, Huang Y, Wu C. *Blood.* 2021 Dec 6;blood.2021013474. DOI: 10.1182/blood.2021013474. PMID: 34871362

*This study establishes a distinct role of intestinal IL-33 in activating platelet by promoting 5-HT release for systemic physiology and inflammation.*

### **Intravenous administration of BCG protects mice against lethal SARS-CoV-2 challenge**

Hilligan KL, Namasivayam S, Clancy CS, O'Mard D, Oland SD, Robertson SJ, Baker PJ, Castro E, Garza NL, Lafont BAP, Johnson R, Ronchese F, Mayer-Barber KD, Best SM, Sher A. *J Exp Med.* 2022 Feb 7;219(2):e20211862.

PMID: 34889942. PMCID: PMC8669500. DOI: 10.1084/jem.20211862

*We show that intravenous but not subcutaneous administration of BCG provides protection against lethal SARS-CoV-2 infection in mice, reducing immunopathology in addition to viral load and thus providing an experimental model for delineating innate mechanisms of resistance against COVID-19.*

### **Fine-tuning of B-catenin in mouse thymic epithelial cells is required for postnatal T-cell development**

Fujimori S, Ohigashi I, Abe H, Matsushita Y, Katagiri T, Taketo MM, Takahama Y, Takada S. *eLife.* 11:e69088 (2022).

PMID: 35042581. PMCID: PMC8769649. DOI: 10.7554/eLife.69088

*By using a recently devised B5t-Cre that is highly specific for thymic epithelial cells (no side effects in the skin hair cells unlike Foxn1-Cre), this paper shows that a limited range of B-catenin expression is required for thymic epithelial cells to generate an optimal microenvironment to support postnatal T-cell development.*

### **mTEC damage risks immune recovery**

Takahama Y. *Journal of Experimental Medicine.* 219:e20212326 (2022). PMID: 34919145. PMCID: PMC8689664. DOI: 10.1084/jem.20212326

*Commentary on a recent study demonstrating that prolonged damage in thymic medullary epithelial cells causes the failure in self-tolerance in newly generated T cells and provokes post-transplant autoimmunity.*

### **Specific impact of B5t on proteasome subunit composition in cortical thymic epithelial cells**

Ohigashi I, Takahama Y. *Cell Reports.* 36:109657 (2021).

PMID: 34496235. PMCID: PMC8442848. DOI: 10.1016/j.celrep.2021.109657

*In response to a recent article reporting that B5t regulates the expression of hundreds of genes in cortical thymic epithelial cells (cTECs) and affects both CD4+ and CD8+ thymocytes by causing oxidative stress in thymocytes, this article demonstrates that, rather than regulating hundreds of genes, 5t has a highly specific impact in cTECs on proteasome subunit composition.*

Continued>>

### **Peptides for T cell selection in the thymus**

Ohigashi I, Matsuda-Lennikov M, Takahama Y. *Peptides*. 146:170671 (2021). PMID: 34624431 DOI: 10.1016/j.peptides.2021.170671

*This review article summarizes recent advances in the study of MHC-associated thymic peptides, focusing on the generation and function of thymoproteasome-dependent peptides specifically displayed by cortical thymic epithelial cells.*

### **Aryl Hydrocarbon Receptor Mechanisms Affecting Chronic Kidney Disease**

Colleen S. Curran, Jeffrey B. Kopp. *Front Pharmacol*. 2022 Feb 14;13:782199. PMID: 35237156 PMCID: PMC8882872 DOI: 10.3389/fphar.2022.782199

*The aryl hydrocarbon receptor (AHR) is a basic helix-loop-helix transcription factor that binds diverse endogenous and xenobiotic ligands, which regulate AHR stability, transcriptional activity, cell signaling and the progression of chronic kidney disease (CKD). We review the roles of AHR in kidney fibrosis, metabolism and the renin angiotensin system to offer insight into CKD pathogenesis and therapies.*

### **Modulation of Macrophage Immunometabolism: A New Approach to Fight Infections**

Gauthier T, Chen W. *Front Immunol*. 2022 Jan 26;13:780839. PMID: 35154105 DOI: 10.3389/fimmu.2022.780839

*In the past decade, modulation of metabolism has been described as critical for macrophages to sustain their functions. Here, we reviewed the role of macrophage immunometabolism during infections and how it could be therapeutically targeted, notably to fight SARS-CoV2 infections.*

### **Differential T cell immune responses to deamidated adeno-associated virus vector**

Bing SJ, Justesen S, Wu WW, Sajib AM, Warrington S, Baer A, Thorgrimsen S, Shen RF, Mazor R. *Mol Ther Methods Clin Dev*. 2022 Mar 10; 24 255-267. PMID: 35211638 PMCID: PMC8829777 DOI: 10.1016/j.omtm.2022.01.005

*We show that the immunogenicity of AAV vectors is enhanced by spontaneous deamidation in individuals with certain HLA II.*

### **Human lymph node immune dynamics as driver of vaccine efficacy: an understudied aspect of immune responses**

Moysi E, Paris RM, Le Grand R, Koup RA, Petrovas C. *Expert Rev Vaccines*. 2022. PMID: 35193447 DOI: 10.1080/14760584.2022.2045198.

*This review describes the contribution of genetic variation, aging, the microbiome and chronic infection on Tfh and B-cell dynamics in LNs and discusses how the study of LN micro-architecture can complement current single-cell analyses and assist the design of improved preventive and therapeutic interventions.*

### **Generation of Single-Domain Antibody-Based Recombinant Immunotoxins**

Fleming BD, Ho M. *Methods Mol Biol*. 2022;2446:489-512. PMID: 35157290 DOI: 10.1007/978-1-0716-2075-5\_25.

*We discuss the design, production, and testing of single-domain antibody-based recombinant immunotoxins.*

### **Development of Glypican-2 Targeting Single-Domain Antibody CAR T Cells for Neuroblastoma**

Li N, Ho M. *Methods Mol Biol*. 2022;2446:451-468. PMID: 35157288 DOI: 10.1007/978-1-0716-2075-5\_23.

*We describe a protocol for generating GPC2-targeted sdAb CAR T cells. The method described here is applicable to the production of CAR T cells derived from all types of sdAbs including VHHs and VNARs.*

### **Preclinical testing of chimeric antigen receptor T cells in neuroblastoma mouse models**

Li N, Nguyen R, Thiele CJ, Ho M. *STAR Protoc*. 2021 Nov 10;2(4):100942. PMID: 34825213 DOI: 10.1016/j.xpro.2021.100942

*We describe steps to implement neuroblastoma metastatic and orthotopic mouse models. Both mouse models can be applied to evaluate other experimental therapies for neuroblastoma.*

### **New Insights into Epigenetic Regulation of T Cell Differentiation**

Dutta A, Venkataganesh H, Love PE. *Cells*. 2021 Dec 8;10(12):3459. PMID: 34943965; PMCID: PMC8700096. DOI: 10.3390/cells10123459

*We summarize novel insights into epigenetic regulation of T cell differentiation in both mice and humans.*

### **Combination Therapy of Hepatocellular Carcinoma by GPC3-Targeted Bispecific Antibody and Irinotecan is Potent in Suppressing Tumor Growth in Mice**

Chen X, Chen Y, Liang R, Xiang L, Li J, Zhu Y, He H, Huang L, Zuo D, Li W, Liang X, Dong S, Hu S, Ho M, Feng M  
Mol Cancer Ther. 2022 Jan;21(1):149-158  
PMID: 34725191 PMCID: PMC8742776 DOI: 10.1158/1535-7163.MCT-20-1025

*We demonstrated that the cell surface proximal bispecific antibody hYP7-OKT3-hFc was superior in terms of potency and the GPC3-targeted bispecific antibody combined with Irinotecan was much potent to control HCC growth.*

### **Circulating T Cells Are Not Sufficient for Protective Immunity against Virulent Francisella tularensis**

Roberts LM, Wehrly TD, Leighton I, Hanley P, Lovaglio J, Smith BJ, Bosio CM  
J Immunol. 2022 Feb 11;ji2100915.

PMID: 35149529 DOI: 10.4049/jimmunol.2100915.  
*Using mouse parabiosis, we determined circulating T cells initially restrict Francisella replication but were ultimately not sufficient to protect against lethal challenge. This finding, in combination with a previous publication showing lung resident T cells are not sufficient, indicates efficacious Francisella vaccines must elicit both resident and circulating T cell responses.*

### **Itaconate indirectly influences expansion of effector T cells following vaccination with Francisella tularensis live vaccine strain**

Roberts LM, Leighton I, Schwarz B, Wehrly TD, Evans TJ, Bosio CM.

Cell Immunol. 2022 Feb 7;373:104485  
PMID: 35149415. DOI: 10.1016/j.cellimm.2022.104485.  
*Mice deficient for itaconate production have quantitative and qualitative improvements in the T cell response after Francisella tularensis infection. Although T cells can take up itaconate, it did not affect their function therefore the impacts of itaconate on the T cell response are indirect via infected APCs.*

### **Impairing RAGE signaling promotes survival and limits disease pathogenesis following SARS-CoV-2 infection in mice**

Jessop F, Schwarz B, Scott D, Roberts LM, Bohrsen E, Hoidal JR, Bosio CM.

JCI Insight. 2022 Jan 25;7(2):e155896.  
PMID: 35076028; PMCID: PMC8855831. DOI: 10.1172/jci.insight.155896.

*SARS-CoV-2 infection leads to severe hypoxia and lethality in*

*K18-hACE2 mice. Inhibition of Receptor for Advanced Glycation End Products (RAGE) signaling following SARS-CoV-2 infection limited inflammation and damage to the pulmonary vasculature and improved survival.*

### **In vitro reconstitution reveals cooperative mechanisms of adapter protein-mediated activation of phospholipase C-1 in T cells**

Wada J, Rathnayake U, Jenkins LM, Singh A, Mohammadi M, Appella E, Randazzo PA, Samelson LE.

J Biol Chem. 2022 Feb 3;3101680.  
PMID: 35124007 DOI: 10.1016/j.jbc.2022.101680.

*We have reconstituted in vitro a critical tetrameric protein complex required for T cell activation, which is comprised of the enzyme PLC-, the soluble adaptors Gads and SLP-76 and the protein binding component of the transmembrane adapter LAT. We demonstrate binding of this protein complex to liposomes and show that formation of this protein complex as well as tyrosine phosphorylation of PLC-are required for optimal activation of this enzyme.*

### **IL-27-producing B-1a cells suppress neuroinflammation and CNS autoimmune diseases**

Choi JK, Yu CR, Bing SJ, Jittayasothorn Y, Mattapallil MJ, Kang M, Park SB, Lee HS, Dong L, Shi G, Caspi RR, Egwuagu CE

Proc Natl Acad Sci USA. 2021 Nov 23; 118(47)  
PMID: 34782464, PMCID: PMC8617509 DOI: 10.1073/pnas.2109548118

*We identified an innate IL-27-producing natural regulatory B-1a cells (i27-Breg) in peritoneal cavity and human umbilical cord blood which suppress encephalomyelitis or uveitis by propagating inhibitory signals that convert conventional lymphocytes to IL-35-secreting regulatory cells and inhibit Lag3+PD-1+ T cells that mediate CNS autoimmune diseases.*

### **Epigenetic regulation of T cell development**

Dutta A, Venkataganesh H, Love PE

Int Rev Immunol. 2021 Dec 30;1-9.  
PMID: 34967703. DOI: 10.1080/08830185.2021.2022661.  
*In this review, we summarize recent findings that have provided new insights into epigenetic regulation of T cell differentiation in both mice and humans.*

Continued>>

### **Phase I Clinical Trial of an Autologous Dendritic Cell Vaccine Against HER2 Shows Safety and Preliminary Clinical Efficacy**

Maeng HM, Moore BN, Bagheri H, Steinberg SM, Inglefield J, Dunham K, Wei WZ, Morris JC, Terabe M, England LC, Roberson B, Rosing D, Sachdev V, Pack SD, Miettinen MM, Barr FG, Weiner LM, Panch S, Stroncek DF, Wood LV, Berzofsky JA

Front Oncol. 2021 Dec 16;11:789078

PMID: 34976830 PMCID: PMC8716407 DOI: 10.3389/fonc.2021.789078

*This publication is a clinical trial report of the phase 1 study testing the safety and immunogenicity of a dendritic cell-based cancer vaccine against HER2 in solid tumors demonstrating intramural collaborative efforts from invention and manufacturing of cellular products to execution of a clinical trial all at the NIH.*

### **Persistent Oxidative Stress and Inflammasome Activation in CD14<sup>+</sup>high CD16<sup>-</sup> Monocytes From COVID-19 Patients**

Lage SL, Amaral EP\*, Hilligan KL, Laidlaw E, Rupert A, Namasvaya S, Rocco J, Galindo F, Kellogg A, Kumar P, Poon R, Wortmann GW, Shannon JP, Hickman HD, Lisco A, Manion M, Sher A, Sereti I.

Front Immunol. 2022 Jan 14;12:799558

PMID: 35095880 PMCID: PMC8795739 DOI: 10.3389/fimmu.2021.799558

*We show that severe forms of COVID-19 are associated with robust and persistent inflammasome activation and oxidative stress response in circulating inflammatory (CD14<sup>+</sup>CD16<sup>-</sup>) blood monocytes from patients. In addition, we found that NLRP3 inflammasome-derived IL-1 secretion by SARS-CoV-2-exposed monocytes in vitro was partially dependent on lipid peroxidation, an oxidative stress process. These findings suggest oxidative stress/NLRP3 signaling pathway as a potential target for host-directed therapy to mitigate early COVID-19 hyperinflammation and also its long-term outcomes.*

# 2022 IIG Workshop

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

**S**ave 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. The hybrid meeting platform will allow attendance to be in-person with a virtual attendance option (at least for the plenary and oral session; options for virtual poster presentations are under investigation).

Stay tuned for future announcements and information, including upcoming program outline and registration.



## IIG Principal Investigators

**Want to highlight your lab on the IIG website?**

Email Maria Parkhurst ([parkhurmm@mail.nih.gov](mailto:parkhurmm@mail.nih.gov)) with your name, link to your individual website (if applicable), area of expertise, and an institute affiliation. Please indicate if your lab participates in clinical research.

Below is a list of areas of expertise for your selection, but you may certainly identify another area if you do not believe any of the following categories are appropriate:

- Allergy and Other Hypersensitivities
- Antigen Recognition and Responses
- Autoimmunity
- Clinical and Human Immunology
- Cytokine Biology
- Immune System Development
- Immunogenetics
- Immunometabolism
- Immunotherapy and Vaccines
- Infectious Disease and Host Response
- Innate Immunity and Inflammation
- Molecular and Structural Immunology
- Mucosal Immunology
- Neuroimmunology
- Systems Immunology
- Transplantation
- Tumor Immunology

# NIH-Sponsored Clinical Trials

## Bench-to-Bedside in action

**H**arnessing fundamental knowledge to advance our understanding of disease and develop novel treatment strategies is a major mission of the NIH. Below are several clinical studies at the NIH Clinical Center that are doing just that.

### **NADPH Oxidase Correction in mRNA-transfected Granulocyte-enriched Cells in Chronic Granulomatous Disease (CGD)**

*CGD is caused by a gene mutation. For people with CGD, their cells cannot kill germs well, so they can get frequent or life-threatening infections. Researchers want to see if a new procedure can help a person's cells kill germs for a short time. It uses messenger RNA (mRNA) to deliver correct instructions for the gene mutation to the cells.*

[Sponsor: NIAID <https://clinicaltrials.gov/ct2/show/NCT05189925?cntry=US&state=US%3AMD&ci->

### **GPC3 Targeted CAR-T Cell Therapy in Advanced GPC3 Expressing Hepatocellular Carcinoma (HCC)**

*A new cancer treatment takes a person's own T cells, modifies them in a laboratory so they can better fight cancer cells, and then gives them back to the person. Researchers want to see if this treatment can help people with a certain type of liver cancer.*

[Sponsor: NCI <https://clinicaltrials.gov/ct2/show/NCT05003895?cntry=US&state=US%3AMD&city=Bethesda&draw=1&rank=50>]

### **Phase II Trial of Combination Anti-PD-1 and Aldesleukin for Metastatic Melanoma and Renal Cell Carcinoma**

*Aldesleukin is used to treat metastatic or advanced melanoma and renal cell carcinoma. Pembrolizumab is used to treat many cancers including melanoma. Researchers want to see if these drugs can be used together to produce better results in people with these types of cancer.*

[Sponsor: NCI <https://clinicaltrials.gov/ct2/show/NCT05155033?cntry=US&state=US%3AMD&city=Bethesda&draw=3&rank=17>]

### **PET Imaging of Cyclooxygenase-2 in Multiple Sclerosis**

*Multiple sclerosis (MS) is an autoimmune disease that has no cure. MRI is the main tool used in the study and treatment of people with MS. A tracer has been developed for cyclooxygenase-2 (COX-2), an enzyme found in the brain during inflammation. Researchers want to explore the role inflammation plays in MS and see if COX-2 is measurable in the brains of people with the disease.*

[Sponsor: NIMH <https://clinicaltrials.gov/ct2/show/NCT05062083?cntry=US&state=US%3AMD&city=Bethesda&draw=1&rank=30>]

# Immunology Interest Group

# SPOTLIGHT

Introducing a new section to the newsletter - the 'IIG Spotlight'! This new section will highlight IIG investigators and members to promote communication and collaboration across the NIH-FDA immunology community. This inaugural edition shines light on Dr. Laurie Krug (NCI/NIH) and Dr. Ronit Mazor (FDA/CBER).

**Dr. Krug is a Stadtman investigator in the HIV and AIDS Malignancy Branch. To learn more about her work visit:**

<https://ccr.cancer.gov/staff-directory/laurie-t-krug>

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

As an Investigator at NCI, I study oncogenic gammaherpesviruses that target B cells so I am interested in how the virus hijacks the host to promote infection and how that can lead to cancer. I also have research projects related to understanding how the virus blocks immune control so we can improve host immune responses with vaccines and immunotherapy.

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

My favorite course in graduate school was Immunology. In both my graduate research and post-doc training I studied herpesviruses that infected immune cells. Immunology has always been intertwined in my viral pathogenesis research. I view immunology through the lens of the virus, fascinated by how herpesviruses have evolved to usurp immune signaling pathways for their own benefit.

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

My PhD advisor, Dr. Philip Pellett, was a patient mentor who taught me to invest time to carefully optimize a new system to yield reproducible results, and hammered in the lesson that there is no such thing as 'bad data' if an experiment is properly controlled. He was also a great role model and was supportive of my goals to have a family while pursuing my career.

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

I think single cell analysis via sequencing and imaging methodologies is going to shift paradigms in virus-host interactions. I expect virus-specific immunotherapies and antibody-targeted drug and CRISPR therapies that target latent herpesviruses will move into patients.

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

The NIH-FDA IIG is an incredibly collegial and collaborative group of scientists. The PIs and trainees are creative, work hard and perform cutting-edge research. I joined a few months before the pandemic, but IIG has maintained a strong virtual presence that has kept me energized.

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

I enjoy hiking and biking with my family, and barre and yoga on my mat. I look forward to returning to travel and attending live music performances.



Laurie T. Krug, Ph.D.

# Immunology Interest Group

# SPOTLIGHT

**Dr. Mazor is an investigator in the Gene Transfer and Immunogenicity Branch in the Office of Tissues and Advanced Therapies of CBER. To learn more about her work visit:**

**<https://www.fda.gov/vaccines-blood-biologics/biologics-research-projects/immunogenicity-gene-therapy-products>**

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

In the past two years, my team members and I have been establishing a translational immunology lab that focuses on immunogenicity of gene therapy products in the Center for Biologics Evaluation and Research in the FDA. Our lab develops platform technologies to investigate, monitor and mitigate the adaptive and innate immunogenicity of AAV vectors.

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

Sitting in class while in ninth grade in Israel, learning for the first time about species variation and natural selection. I vividly remember how my mind went on thinking for a few days after that class, imagining all the scenarios where those rules apply, not only in nature, but pretty much everything I knew. I knew then that I will be a scientist. The realization that I am an immunologist came several years later, during my graduate studies when I realized how powerful, flexible, and yet disciplined T cells can be. I find these properties fascinating and I want to harness these attributes and control them for patient's benefit. Today, I have a keen interest in how immunology affects the outcomes of drugs and gene therapies and what can be done to improve it.



Ronit Mazor, PhD

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

I was fortunate to have several wonderful people and role models that helped me and gave advice throughout my career. However, when I hear the word mentor, I think of Ira Pastan. He was my supervisor during my training at the NCI and under his influence I shaped the vision for my research for years to come. Ira's "bench to bedside" scientific approach as well as his sincere passion for science inspired me to focus on highly translational immunological features of patients and drug design. As a result, I've established a research laboratory at the FDA with an aim to investigate the immunological challenges of cell and gene therapy products.

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

I believe that some of the most interesting findings in science can be found at the intersections of different fields. I think that the next big innovations will come from the NGS, big data and artificial intelligence and their integration with patient's care, patient's response to drugs and their adverse events. This can lead to true personalized medicine and may provide new leads on biochemical signaling that are unique to specific genetic populations.

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

I have been a member of the NIH-FDA Immunology community since 2010, initially as a graduate student in the NIH Graduate Partnership Program (GPP), later as a post-doctoral fellow in the NCI and now as a principal investigator in CBER/FDA. I think that not only does our community advance science and opportunities, but it also brings together great minds from many immunology related disciplines to promote a wide perspective that can solve problems that could not be solved by a single field.

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

I like to spend my time with my family, go on trips and explore new places. I am also part of an amateur competitive catch ball team. Catch ball is a team sport, similar to volleyball, that brings out my competitive side in a female empowering environment.



# Immunology Interest Group

# SEMINAR SERIES

## February 2022



February 2, 2022

**Jennifer Gommerman**

Fantastic IgA plasma cells and where to find them



February 9, 2022

**Doreen Cantrell\*\***

Environmental control of T lymphocytes



February 16, 2022

**Greg M. Delgoffe**

Metabolic liabilities and opportunities in cancer immunology



February 23, 2022

**Philippa Marrack**

B cells, viruses and autoimmunity

## March 2022



March 2, 2022

**Nicola Ternette**

Driving antigen discovery by integrating proteogenomics and *de novo* peptide sequencing strategies



March 9, 2022

**Catherine Blish**

Seq-ing answers to COVID-19



March 16, 2022

**Montserrat Anguerra**

X-chromosome inactivation in immune cells: understanding the female-bias of SLE disease



March 23, 2022

**Arthur Weiss**

Controlling a hierarchy of kinases involved in TCR ligand discrimination



March 30, 2022

**Ronen Alon**

Integrin cues for lymphocyte trafficking and differentiation: facts and puzzles

# 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.

# Join the List Serve! Immunology Interest Group

Share with new colleagues and trainees that  
join the lab:

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

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