NIH-FDA IIG NEWSLETTER

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

JANUARY 2024

PUBLICATIONS

TGF-beta uncouples glycolysis and inflammation in macrophages and controls survival during sepsis

Gauthier T, Yao C, Dowdy T, Jin W, Lim YJ, Patiño LC, Liu N, Ohlemacher SI, Bynum A, Kazmi R, Bewley CA, Mitrovic M, Martin D, Morell RJ, Eckhaus M, Larion M, Tussiwand R, O'Shea JJ, Chen W.
Sci Signal. 2023 Aug 8;16(797).
doi: 10.1126/scisignal.ade0385. PMID: 37552767.

Usually, glycolytic metabolism results in an inflammatoryA phenotype in immune cells, but we found that macrophages activated by the cytokine TGF-beta had a glycolytic metabolism but were less inflammatory. TGF-beta decreased the survivalA of mice with sepsis, which was associated with increased coagulation, a complication of sepsis that can lead to organ dysfunction. Thus, targeting TGF-beta may improve survival and reduce coagulation-associated complications in septic patients.A

T cell intrinsic STAT1 signaling prevents aberrant Th1 responses during acute toxoplasmosis

Schultz AB, Kugler DG, Nivelo L, Vitari N, Doyle LP, Ristin S, Hennighausen L, O'Shea JJ, Jankovic D, Villarino AV.
Front Immunol. 2023 Jul 25;14:1212190.
doi: 10.3389/fimmu.2023.1212190. PMID: 37559725.

We showed that T cell intrinsic STAT1 signaling is required for control of inflammation during acute infection with Toxoplasma gondii. Our findings provide insights on the anti-inflammatoryA properties of STAT1, highlighting its role in shaping the character ofATh1-type responses.A

Pro-regenerative biomaterials recruit immunoregulatory dendritic cells after traumatic injury

Lokwani R, Josyula A, Ngo TB, DeStefano S, Fertil D, Faust M, Adusei KM, Bhuiyan M, Lin A, Karkanitsa M, Maclean E, Fathi P, Su Y, Liu J, Vishwasrao HD, Sadtler K.
Nat Mater. 2024 Jan;23(1):147-157.
doi: 10.1038/s41563-023-01689-9. Epub 2023 Oct 23. PMID: 37872423.

After traumatic muscle injury and medical device implantation, there is a differential recruitment of dendritic cells to the injuryA site. Pro-regenerative biomaterials induce NK cell mediated secretion of XCL1 and recruitment of cDC1s that are correlated with Treg recruitment (both CD4 and CD8) and required for maintenance of post-injury tissue development.A

Pan-Cancer Analysis of Patient Tumor Single-Cell Transcriptomes Identifies Promising Selective and Safe Chimeric Antigen Receptor Targets in Head and Neck Cancer

Madan S, Sinha S, Chang T, Gutkind JS, Cohen EEW, Schäffer AA, Ruppin E.
Cancers (Basel). 2023 Oct 8;15(19):4885.
doi: 10.3390/cancers15194885. PMID: 37835579.

By analysis of single-cell transcriptomics data, we identified new candidate cell-surface protein targets for CAR-T therapy in head-and-neck cancer.A

SARS-CoV-2 antibodies recognize 23 distinct epitopic sites on the receptor binding domain

Jiang J, Boughter CT, Ahmad J, Natarajan K, Boyd LF, Meier-Schellersheim M, Margulies DH.
Commun Biol. 2023 Sep 19;6(1):953.
doi: 10.1038/s42003-023-05332-w. PMID: 37726484.

We examined 3D structures of >400 antibodies (Abs) that bind SARS-CoV-2 spike protein, identified 23 distinct Ab-binding regions, and established the relation between different SARS-CoV-2 variants and the 23 antibody-binding regions. The insights from this study may contribute to the development of new vaccines and antibody therapies against future virus and could aid in studies to define antibody-pathogen interactions.A

The background depicts three-dimensional renderings of reconstructed neurons obtained from living brain slices. The diversity in color and shape represents the wide variety of neuronal subtypes that make up the human brain. Credit: THE KAROLINSKA INSTITUTE WITH THE ALLEN INSTITUTE FOR BRAIN SCIENCE. (https://www.science.org/doi/10.1126/science.adl0913)

A robust pipeline for high-content, high-throughput immunophenotyping reveals age- and genetics-dependent changes in blood leukocytes

Liechti T, Van Gassen S, Beddall M, Ballard R, Iftikhar Y, Du R, Venkataraman T, Novak D, Mangino M, Perfetto S, Larman HB, Spector T, Saeys Y, Roederer M.
Cell Rep Methods. 2023 Oct 23;3(10):100619.
doi: 10.1016/j.crmeth.2023.100619. PMID: 37883924.

Here we describe our high-throughput, high-dimensional flowA cytometry sample processing and data analysis pipeline which enabled us to measure >3000 PBMC samples with 192 Samples per experiment. Our pipeline ensures minimal technicalAvariation and rapid unbiased discoveries in large flow cytometry datasets as demonstrated by the herein described unprecedented insights into the genetic and environmental regulation of the human immune system.A

Route of Francisella tularensis infection informs spatiotemporal metabolic reprogramming and inflammation in mice

Jessop F, Schwarz B, Bohrnsen E, Bosio CM.
PLoS One. 2023 Oct 26;18(10):e0293450.
doi: 10.1371/journal.pone.0293450. PMID: 37883420.

In this study by Jessop et al, the murine metabolic response to Francisella tularensis infection was compared between intradermal or pulmonary exposures. Temporal differences in metabolic reprogramming as well as active manipulation of redox metabolism distinguished pulmonary exposure from intradermal exposure and was associated with more rapid disease progression.A

Camel nanobody-based B7-H3 CAR-T cells show high efficacy against large solid tumours

Li D, Wang R, Liang T, Ren H, Park C, Tai CH, Ni W, Zhou J, Mackay S, Edmondson E, Khan J, Croix BS, Ho M.
Nat Commun. 2023 Sep 22;14(1):5920.
DOI: 10.1038/s41467-023-41631-w. PMID: 37739951.

Rational design of chimeric antigen receptor T (CAR-T) cells based on recognizing antigenic epitopes capable of evoking the most potent CAR activation is an important objective in optimizing immune therapy. In this study, the authors present compelling evidence for developing camel VHH nobody-based CAR-T cells that target novel epitopes on B7-H3 (CD276), highlighting their crucial role in achieving potent antitumor activity against large solid tumors.A

The IgG4 hinge with CD28 transmembrane domain improves V_HH-based CAR T cells targeting a membrane-distal epitope of GPC1 in pancreatic cancer

Li N, Quan A, Li D, Pan J, Ren H, Hoeltzel G, de Val N, Ashworth D, Ni W, Zhou J, Mackay S, Hewitt SM, Cachau R, Ho M.
Nat Commun. 2023 Apr 8;14(1):1986.
DOI: 10.1038/s41467-023-37616-4. PMID: 37031249.

Addressing the significant challenge of heterogeneous antigen expression in solid tumors, this paper outlines our engineering of potent CAR-T cells targeting membrane-distal epitopes on glypican-1 (GPC1), a new target in pancreatic cancer. Our studyA highlights the effectiveness of a camelAV_HH nanobody-based CAR-T engineered with an IgG4 hinge and CD28 transmembrane domain, achieving tumor regression in low-antigen-density pancreatic cancer models.A

Identification of nurse shark V_{NAR} single-domain antibodies targeting the spike S2 subunit of SARS-CoV-2

Buffington J, Duan Z, Kwon HJ, Hong J, Li D, Feng M, Xie H, Ho M.
FASEB J. 2023 Jun;37(6):e22973.
doi: 10.1096/fj.202202099RR. PMID: 37191949.

A shark V_{NAR} single-domain antibody S2A9 targeting the spike S2 subunit of SARS-COV-2 was isolated by phage displayA technology and showed broad neutralization activity against most variants of concern of SARS-COV-2 from alpha to omicron.A

IL6 suppresses vaccine responses in neonates by enhancing IL2 activity on T follicular helper cells

Parvathaneni S, Yang J, Lotspeich-Cole L, Sakai J, Lee RC, Akkoyunlu M.
NPJ Vaccines. 2023 Nov 8;8(1):173.
doi: 10.1038/s41541-023-00764-1. PMID: 37938563.

In this study, we showed that, unlike in adults, IL-6 inhibits T follicular helper (Tfh) cell generation by increasing IL-2 production and enhancing IL-2 receptor expression in Tfh cells. The unveiling of IL-6-mediated suppression of neonatalAvaccine responses that involve enhanced IL-2 activity on Tfh cells may have implications for the development of vaccines targeting early age.A

Continued>>

Too Much of a Good Thing: Extended Duration of Gut Microbiota Depletion Reverses Protection From Experimental Autoimmune Uveitis

Salvador R, Horai R, Zhang A, Jittayasothorn Y, Tang J, Gupta A, Nagarajan V, Caspi RR.
Invest Ophthalmol Vis Sci. 2023 Nov 1;64(14):43.
doi: 10.1167/iovs.64.14.43. PMID: 38019490; PMCID: PMC10691388.

Gut microbiota may play dual roles in uveitis development: they promote the development of experimental autoimmune uveitis (EAU), but also help maintain gut intraepithelial lymphocytes (IELs) that have regulatory function against autoreactive T cells. We propose that the progressive loss of the IEL population during long-term antibiotic treatment reverses the EAU-ameliorating effects of microbiota depletion.A

TCR ligand potency differentially impacts PD-1 inhibitory effects on diverse signaling pathways

Chan W, Cao YM, Zhao X, Schrom EC, Jia D, Song J, Sibener LV, Dong S, Fernandes RA, Bradfield CJ, Smelkinson M, Kabat J, Hor JL, Altan-Bonnet G, Garcia KC, Germain RN.
J Exp Med. 2023 Dec 4;220(12):e20231242.
doi: 10.1084/jem.20231242. PMID: 37796477.

PD-1 engagement byA T cells inhibits distinct antigen-evoked signals in a non-linear manner strongly influenced by the nature of available TCR ligands.A

Gut-liver axis calibrates intestinal stem cell fitness

Kim G, Chen Z, Li J, Luo J, Castro-Martinez F, Wisniewski J, Cui K, Wang Y, Sun J, Ren X, Crawford SE, Becerra SP, Zhu J, Liu T, Wang S, Zhao K, Wu C.
Cell. 2024 Jan 22:S0092-8674(24)00003-5.
doi: 10.1016/j.cell.2024.01.001. Epub ahead of print. PMID: 38280375.

The gut and liver reciprocally communicate to control gut homeostasis and tissue repair during health and diseases. Kim et al. demonstrate that liver-derived soluble factor pigment epithelium-derived factor (PEDF) restrains intestinal stem cellA (ISC) expansion, suggesting that the gut-liver axis calibrates ISC fitness for intestinal homeostasis.A

Immune determinants of CAR-T cell expansion in solid tumor patients receiving GD2 CAR-T cell therapy

Kaczanowska S, Murty T, Alimadadi A, Contreras CF, Duault C, Subrahmanyam PB, Reynolds W, Gutierrez NA, Baskar R, Wu CJ, Michor F, Altreuter J, Liu Y, Jhaveri A, Duong V, Anbunathan H, Ong C, Zhang H, Moravec R, Yu J, Biswas R, Van Nostrand S, Lindsay J, Pichavant M, Sotillo E, Bernstein D, Carbonell A, Derdak J, Klicka-Skeels J, Segal JE, Dombi E, Harmon SA, Turkbey B, Sahaf B, Bendall S, Maecker H, Highfill SL, Stroncek D, Glod J, Merchant M, Hedrick CC, Mackall CL, Ramakrishna S, Kaplan RN.
Cancer Cell. 2024 Jan 8;42(1):35-51.e8.
doi: 10.1016/j.ccell.2023.11.011. Epub 2023 Dec 21. PMID: 38134936.

Chimeric Antigen Receptor T cell (CAR-T) therapy targeting GD2 in osteosarcoma and neuroblastoma in a Phase I clinical trialA shows feasibility and safety but limited efficacy. Transcriptomic, proteomic, and epigenetic analyses of baseline, product and post treatment patient samples demonstrates myeloid and T cell phenotypes associated with CAR-T expansion.A

Autoimmunity: Are we asking the right question?

Matzinger P.
Front Immunol. 2022 Nov 3;13:864633.
doi: 10.3389/fimmu.2022.864633. PMID: 36405714; PMCID: PMC9671104.

This essay challenges the long-standing question in autoimmunity – "what causes a break in self-tolerance", by providing Danger Model-based suggestions that manyA autoimmune diseases might be due to defects in normal tissue physiology.A

Transient autoantibodies to danger signals

Shaw ER, Matzinger P.
Front Immunol. 2023 Jan 18;14:1046300.
doi: 10.3389/fimmu.2023.1046300. PMID: 36742299; PMCID: PMC9889632.

The Danger Model predicts that transient cytokines that can activate APCs are particularly logi-cal targets for an autoantibody response, and that a short-lived autoantibody response to dan-ger signals might occur during any infection/ injury in otherwise healthy individuals. Depending on context and neutralization activity, anti-danger signal autoantibodies may benefit the host by restraining immunopathology or, conversely, provoke an immunodeficiency or autoimmune disease.A

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Albert Bendelac (1956-2023)

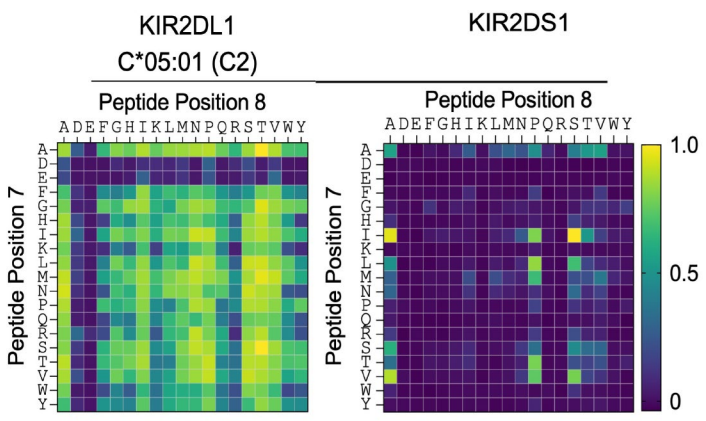
Matzinger P, Lantz O.
Immunity. 2023 Nov 14;56(11):2457-2458.
doi: 10.1016/j.immuni.2023.10.003. Epub 2023 Oct 23. PMID: 37875113.

A heartfelt obituary honoring a dear friend and humble pioneer in immunology.A

Innate receptors with high specificity for HLA class I-peptide complexes

Sim MJW, Brennan P, Wahl KL, Lu J, Rajagopalan S, Sun PD, Long EO.
Sci Immunol. 2023 Sep 8;8(87):eadh1781.
doi: 10.1126/sciimmunol.adh1781. PMID: 37683038.

Inhibitory killer-cell Ig-like receptors (KIR) on NK cells are known as strong binders to HLA-C. We show that activating KIR, heretofore considered weak HLA-C binders, are not weak but peptide specific. Malcolm is now Group Leader at Oxford University (malcolm.sim@immonc.ox.ac.uk).A



*Inhibitory KIR (left) and activating KIR (right) binding to a library ofA peptides presented by HLA-C*05:01.A*

Preclinical and clinical studies of a tumor targeting IL-12 immunocytokine

Minnar CM, Lui G, Gulley JL, Schlom J, Gameiro SR.
Front Oncol. 2024 Jan 8;13:1321318.
doi: 10.3389/fonc.2023.1321318. PMID: 38260854; PMCID: PMC10802843.

This review discusses the current studies involving the tumor-targeted fusion protein NHS-IL12, and illustrates the mounting preclinical and clinical evidence to support its use as an integral component of combination therapies for the treatment of solid tumors, including in combination with immune checkpoint blockade and other treatment modalities.A

Impact of HLA class I functional divergence on HIV control

Viard M, O'hUigin C, Yuki Y, Bashirova AA, Collins DR, Urbach JM, Wolinsky S, Buchbinder S, Kirk GD, Goedert JJ, Michael NL, Haas DW, Deeks SG, Walker BD, Yu X, Carrington M..
Science. 2024 Jan 19;383(6680):319-325.
doi: 10.1126/science.adk0777. Epub 2024 Jan 18. PMID: 38236978.

HLA allotypes can differ by few or by many (often radical) amino acid changes which, depending on the complementarity of allotype combinations, should lead to fitness differences between heterozygotes of different allotypic composition. However, the predicted fitness differences have proven difficult to demonstrate from HLA gene sequences. Peptide binding profiles of individual HLA allotypes can be used to predict function more accurately than HLA gene divergence and offer a novel approach to defining heterozygous divergence. This study developed a functional divergence metric that measures pairwise complementarity of allotype-associated peptide binding profiles. The metric predicts immune breadth at the peptide level rather than gene level and redefines HLAA heterozygosity as a continuum differentially affecting disease outcome. Greater functional divergence for pairs of HLA-A and/A or HLA-B allotypes was associated with slower AIDS progression and independentlyAwith enhanced viral load control. FunctionalA divergence may be used to predict response to additional infections, vaccination, immunotherapy, and other contexts where HLA heterozygote advantage occurs.A

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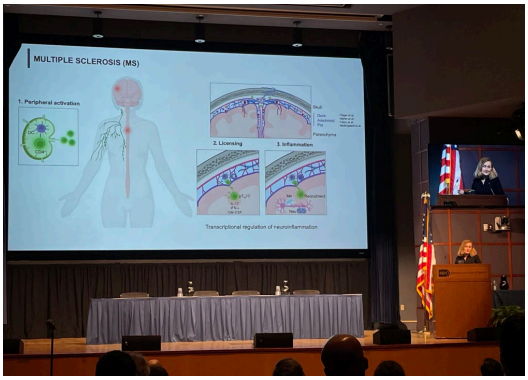
HIGHLIGHTS

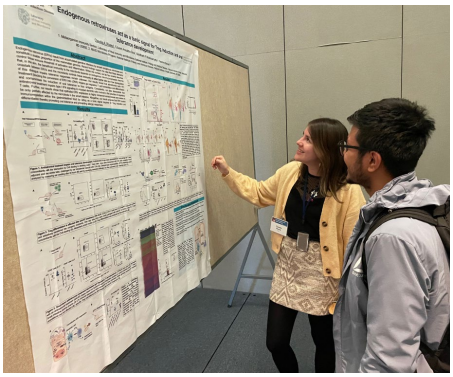
The inaugural **IIG-FAES Symposia on Barrier Immunity** showcased a diversity of immunological research, led by a likewise diverse ensemble of immunologists – enlightening our understanding and imagination of the immunological science.

Special thanks to Stefan Muljo & P'ng Loke for leading the symposia organization! The newsletter team is grateful for all the photo submissions.

Edna Cukierman (Fox Chase)

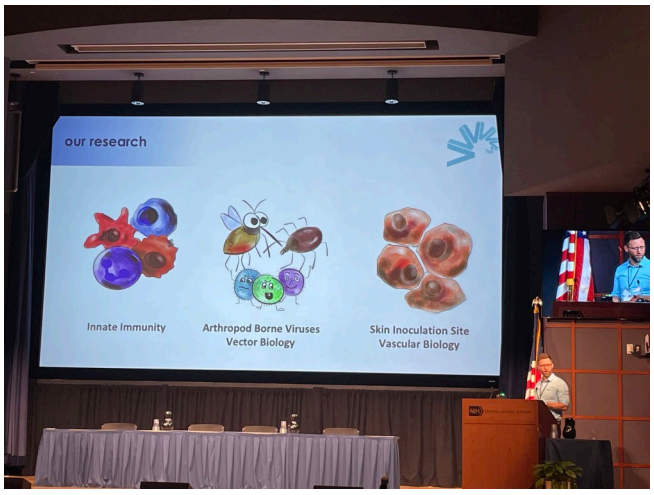


Vanja Lazarevic (NCI)

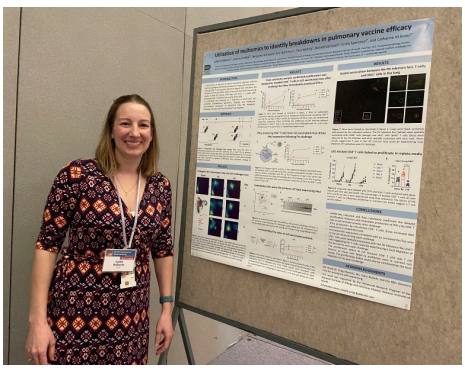


Claudia Rivera (NIAID)

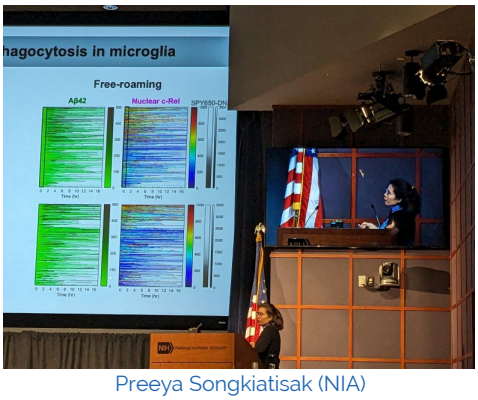
Aurora Kraus (NICHD)



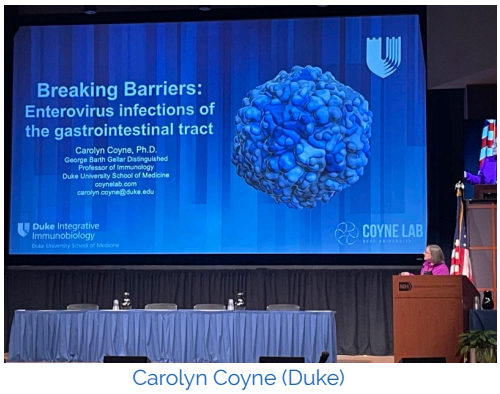
Clive McKimmie (U Leeds)



Lydia Roberts (NIAID)



Preeya Songkiatisak (NIA)



Carolyn Coyne (Duke)

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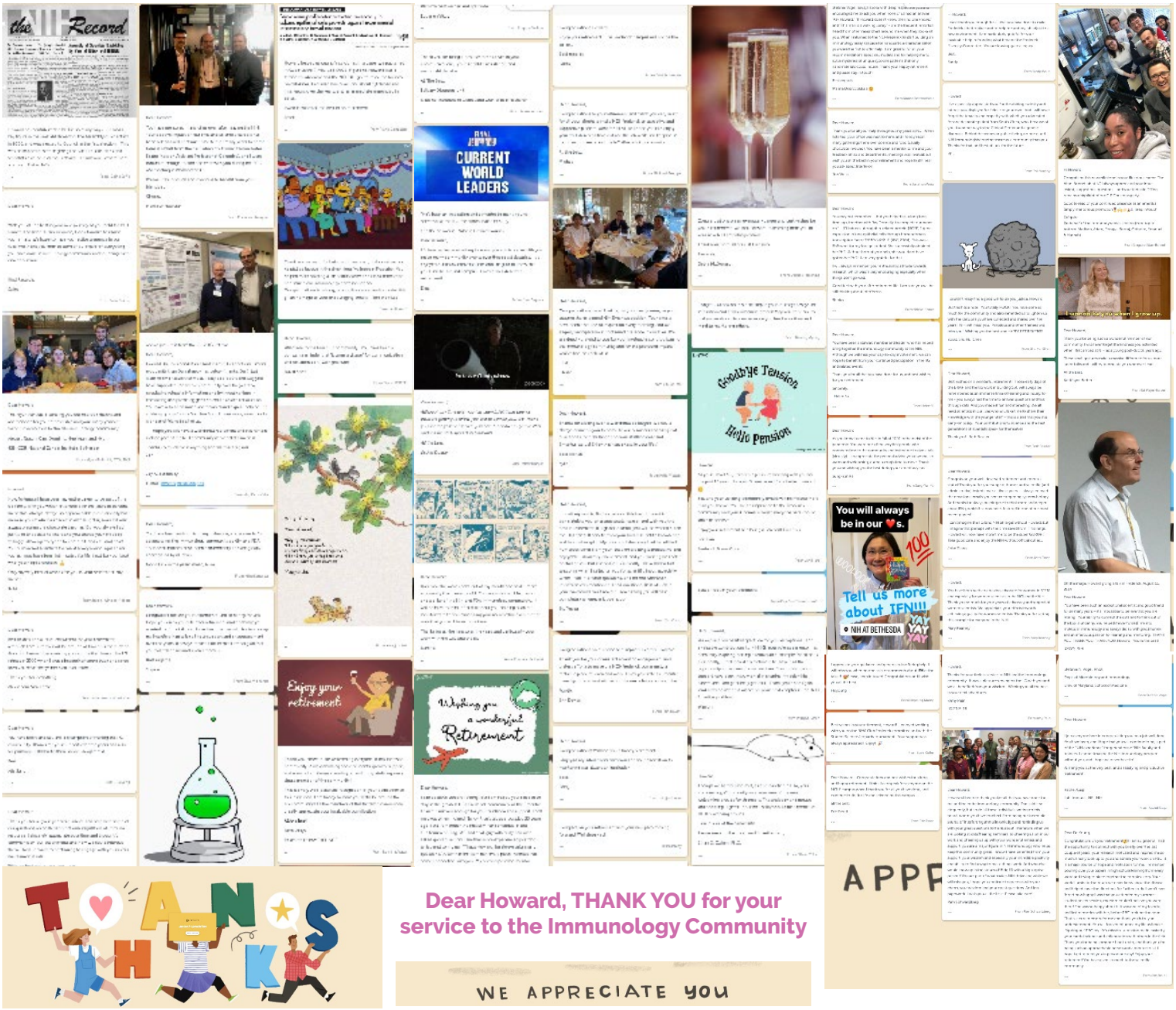
IIG's beloved Howard Young is becoming emeritus!

Congratulations Howard!

The well-populated kudosboard symbolizes how impactful you are to the immunology community (snapshots below, details at https://www.kudoboard.com/boards/2b7vPFce). For a Festschrift honoring Howard by the Journal of Interferon & Cytokine Research please see https://www.liebertpub.com/toc/jir/42/12.

The IIG Newsletter team would like to express our special thanks to Howard for all the support, and we are looking forward to continued inspirations from Howard.



Snapshots as of February 4, 2024

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Immunology Interest Group

SPOTLIGHT

Dr. Gorman is a principal investigator in the Division of Viral Products, Office of Vaccines Research and Review, Center for Biologics Evaluation and Research, FDA.

Jason Gorman, Ph.D.

Tell us about your science.

Our group applies structural biology to visualize antibodies and viral proteins at an atomic level. This approach enables us to understand the intricacies of immune responses and dissect the molecular interplay between vaccines, hosts, and viruses. We delve into the nuances of how antibodies, both effective and less so, are initially triggered, how they adapt alongside evolving viruses, and the mechanisms through which viruses manage to escape immune defenses. All of this structural information can be leveraged to guide us in devising medical countermeasures. We have a particular interest in HIV-1 and Lassa virus, both notorious for their heavy glycosylation and the significant challenges they pose to the immune system. Our work, in detailing how antibodies effectively target the glycoproteins of these viruses, not only advances our knowledge in the specific areas of HIV-1 and Lassa virus but it also sheds light on broader aspects of viral evolution, antibody behavior, and antigen design. Overall, by understanding immune responses to natural infection and vaccination at an atomic level, we are able to better inform strategies to rationally design, evaluate, and regulate effective vaccines.

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

I have always been interested in understanding how things work at a fundamental level. My initial exposure to structural biology was a pivotal moment; I immediately knew it was a field I wanted to pursue. With each new structure, the rationale behind other experimental results all seemed to fall into place and make sense. Applying structural biology to vaccines and immune responses presents more complex challenges, but it's very rewarding to see how rapidly results from basic structural science in immunology can advance vaccine development and make a direct impact on people's health.

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

Throughout my career, from my days as a technician, through graduate school, my postdoctoral work, and beyond, I have been incredibly lucky to work alongside excellent mentors and colleagues. The diversity of my mentors has been particularly wonderful, each approached science from such different angles and I've learned unique things from each of them. The one common trait they all shared was an undeterrable enthusiasm for science and that kind of energy is great to be around when you're faced with really difficult challenges. Whenever I find myself stuck on a problem, I consider how each of them might handle it and this often spurs me to come up with four or five completely different approaches to try.

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

The easy answer here is AI and machine learning. In structural biology, we witnessed the impact of AlphaFold2's arrival a few years ago, which marked a tremendous leap forward. It has unlocked so many new research avenues that were previously just not possible. The volume of data available across so many fields is increasing at unprecedented rates and one of the biggest challenges lies in figuring out different ways to use this data effectively. As AI and machine learning tools become increasingly more accessible, there are going to be more and more significant breakthroughs and applications, and each of those will likely branch and compound to more innovations.

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

It's that those in the community have a great sense of camaraderie and spirit when it comes to helping one another out and advancing each other's science in general. It's incredibly helpful to receive feedback from colleagues who, while not in my exact field, are experts in the broader subject area and can offer informed and diverse perspectives.

How do you spend your free time?

I have two wonderful young kids, so they take up just about every moment I'm out of the lab. We go for walks, to playgrounds, and run around the house a lot. They are just full of energy, creativity, and curiosity when learning just about anything. This really heightens my appreciation for my work as a scientist, where I can pursue my own curiosities.

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Immunology Interest Group SPOTLIGHT

Dr. Alexander Zhovmer serves as a Principal Investigator in the Laboratory of Immunobiochemistry, Center for Biologics Evaluation and Research, FDA. To learn more about his work visit: https://www.fda.gov/vaccines-blood-biologics/biologics-research-projects/novel-and-emerging-therapies-food-allergy.

Alexander Zhovmer, Ph.D.

Tell us about your science.

My group uses animal models to study perspective immunotherapies for food allergy, trying to uncover mechanisms of coordinated actions of immune cells in tissues.

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

I became interested in immunology during my master's studies, working on cancer immunology at the Institute of Clinical Immunology in Novosibirsk. During my PhD and postdoctoral work, I studied molecular mechanisms of gene expression and cell signaling at the Institute of Genetics and Molecular and Cellular Biology in Illkirch, and at the Memorial Sloan Kettering Cancer Center in New York. I was able to combine these research experiences, studying basic mechanisms of immune cell motility and cell polarization during my work with Dr. Robert Adelstein at the National Heart, Lung, and Blood Institute, NIH.

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

My mentor, Dr. Robert Adelstein, and my colleague, Dr. Erdem Tabdanov, they both taught me perspective-taking in research.

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

Immunotherapy for allergy and autoimmune diseases.

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

People and their stories.

How do you spend your free time?

Playing sports and reading.

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Immunology Interest Group

SPOTLIGHT

Dr. West is a staff scientist in the Laboratory for Complement and Inflammation Research (led by Claudia Kemper) at the National Heart, Lung, and Blood Institute (NHLBI), NIH.

Tell us about your science.

I'm interested in better understanding how the complement system, both systemic liver-derived complement and cell-intrinsic complement (intracellular complement-the complosome) drives and regulates T cell responses (CD4, CD8 and gamma-delta T cells) during immune homeostasis, infection, and autoimmunity. While it is broadly acknowledged that complement plays an important role in inflammatory conditions, it is less understood how complement influences T cell activities during inflammatory responses in vivo. I'm particularly interested in how complement influences tissue-specific T cell immunity including T cell induction and contraction programs, T cell-mediated tissue repair, and T cell memory development and maintenance. I think that understanding these processes will help to identify novel therapeutic targets and may also shed light on strategies to develop more effective CAR T cell therapies for cancer.

Erin West, Ph.D.

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

I began college convinced that I was most interested in physics and math and wanted to be an engineer. However, I quickly realized that my favorite classes were chemistry and biology. I was lucky enough to take an intense immunology class during college that was based on case studies and primary literature (instead of a textbook) where Scottish professor Dr. Roderick MacLeod enthusiastically demonstrated how immunology plays an important (and complicated!) role in human health. It was by far the best class I have ever taken, and I've been hooked on understanding/studying Immunology ever since.

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

I have been very lucky to have multiple great mentors throughout my career. A post-baccalaureate experience at Johns Hopkins in the lab of Dr. John McDyer really developed my independence as a researcher and also convinced me to go the PhD route. My current research is really at the intersection of infection and complement, and my graduate student advisor, Dr. Rafi Ahmed (a viral immunologist), and my current mentor, Dr. Claudia Kemper (a complementologist), have both played major roles in my decision process for focusing on this research area. Through them, combined, I have learned how to work independently, follow the data (even if the results are unexpected), ask good questions, and most importantly they have both passed down their infectious love of science and drive to understand the "big picture".

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

While it's hard to predict the future of science, I think that there will be significant advances in neuroimmunology, tissue-specific responses, obesity/microbiome and more emphasis on understanding immune response differences between the sexes. Ideally more cross-discipline studies will become more of the norm and will help propel research forward.
I'm a bit biased, but I'd also like to think that new insights into complement will help to increase and expand the development and successful use of complement targeting therapeutics to both rare diseases and more common inflammatory diseases.

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Immunology Interest Group SPOTLIGHT

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

The NIH-FDA Immunology community is really one of a kind. While labs at the NIH can sometimes feel a bit isolated (by institute/building/location etc.), the NIH-FDA immunology community does a great job of bridging this gap and bringing the community together, providing ample resource and expertise sharing, opportunities for collaborations, while also organizing engaging seminars and symposiums/workshops that foster community interaction and scientific discussions.

How do you spend your free time?

When I have free time, you'll find me out trail running, or doing activities (like hiking, playing board games, camping) with my children, husband and crazy dog.

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Immunology Interest Group

SPOTLIGHT

Dr. Jonathan Ashwell is a senior investigator in the Laboratory of Immune Cell Biology, NCI/CCR. To learn more about his work visit: https://irp.nih.gov/pi/jonathan-ashwell

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

Jonathan Ashwell, MD.

My father, Gilbert Ashwell, was a biochemist in the then National Institute of Arthritis, Metabolism, and Digestive Diseases, so I was exposed to both scientific research and the NIH at a very young age. As a child, on weekends I would often accompany him to the lab, where I entertained myself with buffered solutions containing pH-sensitive dyes. As I grew, we would discuss his work (the "problem" to be solved) at an age-appropriate level, which I very much enjoyed. Having said that, my path to a scientific career was far from preordained. I had a broad range of interests as I entered college, so I played the field by splitting coursework between pre-med science requirements and humanities. In the end, I found the sciences to be more satisfying and majored in chemistry. Although I had partly differentiated, I was still unsure of my goals (medicine or science), so I applied to medical school because, as my father advised, an MD gives you more flexibility than a PhD. I actually enjoyed medical school, especially its academic aspects, but to make a final decision I had to do a medical residency. Within a year I realized I would not be satisfied purely with patient care, and having developed an interest in endocrinology and immunology I was delighted to learn of a marvelous (and unfortunately now defunct) NIH program offering basic science fellowships to MDs. The beauty of the position (medical staff fellow) was that it carried its own resources, FTE and salary, so if accepted you could choose any participating NIH laboratory that would have you. I was selected for interviews, and was amazed when I ultimately matched with the NIAID Laboratory of Immunology (LI), whose Chief was Bill Paul. I chose to work with Ron Schwartz, who was trying to understand the three body problem of T cell antigen recognition (the antigen, the restricting MHC molecule, and the then unidentified receptor). At that time (1981), the field of immunology was entering an era of explosive growth, and the members of the LI were at the forefront. My fellow postdocs were (and remain) an amazing group, many of them going on to becoming immunological "household names", and the pace and breadth of discovery was very exciting. By the second year I knew I wanted a career in basic immunology research, and few years later I was fortunate enough to obtain a tenure-track position in the NCI, and, ultimately, formed the Laboratory of Immune Cell Biology. Although I'm not suggesting they are for everyone, there are a few basic research principles I have followed over the years. One is that the scientific questions (problems) you address should begin with the biology. By that I mean start with a biological phenomenon of interest and try to understand its basis. Another is that you should not be "technique limited". Use the best strategies and technologies you can – imaging, genetically altered animal models, "omics", etc. – and if your lab does not have the capabilities, collaborate with another that does. Finally, don't assume that the prevailing wisdom is correct. Several of our most impactful projects began with the failure of a control that we knew "couldn't fail". If you make an observation that's impossible, you're probably doing something wrong. But sometimes, if you suspend disbelief and consider that the "wrong" answer might be right, you'll find you've stumbled onto an entirely new way of understanding a bit more of the world.

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

Science is advancing at a seemingly accelerating clip, and tools that weren't conceived of even a handful of years ago now allow us to replace Gedankenexperiments (thought experiments) with actual data. The field of candidates is crowded, but I think artificial intelligence is likely to have an extraordinarily profound and paradigm-altering effect on scientific research (and everything else) within that span of time. I'm not speaking of large language models and generative AI such as ChatGPT, as intriguing as that is, but of scalable machine learning that reveals unexpected patterns and relationships that can only be detected when applied to enormous datasets, and to even produce testable hypotheses and predictions. Like monoclonal

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antibodies, advances in molecular biology, and genetically-engineered animal models in the late 20th century, and bioinformatics and gene editing in this, but in an even more profound way, I suspect that rapid advances in AI will alter how research is conducted in ways we can't imagine.

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

At the institutional level the concept of mentoring seems to have become formalized as an actively pursued and quantifiable activity. Evaluation committees routinely use the number of trainees that have gone on to successful careers as a metric of success. In reality, most postdocs start in their mid-to-late 20's, far along in their development, and their success will largely be determined by their character and talents. Having said that, a good mentor can certainly help them make the most of their potential. This isn't exactly cutting edge, but I think the basis of being a good mentor is being a good role model, especially for younger trainee's. Certainly, as an MD with a mostly clinical background, everything I learned about basic research, from how to address scientific questions to what successful labs looks like, was not taught but was gleaned from the examples set by my mentor and other PIs I respected. The specific knowledge gained and advice received as a trainee are of course valuable, but being exposed to a sound scientific environment during that period can have a profound effect on the trajectory of one's scientific career.

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?

By "we" I assume you mean those of us at the NIH acting as individuals. Obviously there are major efforts toward this end being made by (some) states, the federal government, health organizations, etc., and if given the opportunity we can participate. But for most of us that don't, we can still provide detailed and nuanced information about scientific and medical issues to those with whom we interact. A number of years ago I was present when someone related as personal knowledge that doctors conspired with pharmaceutical companies to perform clinical trials with anti-cancer therapies they knew wouldn't work. Others seemed prepared to believe him, so I (politely) explained that I was a scientist at the National Cancer Institute, what he was saying was simply untrue, and described the rigor with which clinical trials are approved and conducted. In our now post-COVID-19 world things go differently, but he backed off and the others listening were satisfied. We all have such small but potentially impactful opportunities, and shouldn't refrain from rebutting misinformation, and especially disinformation, with facts.

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

Just before I began my postdoctoral fellowship I became fascinated with the then new "microcomputers". I bought an Apple II+, taught myself 6502 assembly language, began coding, and I've never stopped. Programming requires many of the same problem solving skills as research, but unlike the latter, success results in instant gratification. As for time management, I do my best to avoid procrastination. When something unexpected or unwelcome intrudes (like endless notifications of required "refresher courses"), I deal with it right away and then get back to work (until the next one arrives).

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

I don't think the NIH/FDA immunology community needs my advice, they are doing just fine. I will say that I am not aware of any other immunology-oriented community that approaches ours in size, resources, or scope, and it has been my pleasure and privilege to interact with and learn from so many of its members.

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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.

A phase 1/2 dose-escalation trial of long-acting recombinant human IL-7 for idiopathic CD4 lymphopenia. PI: Andrea Lisco, M.D., Ph.D. – HIV Pathogenesis Section, NIAID, DIR.

Background: Idiopathic CD4 lymphopenia (ICL) is a heterogeneous clinical syndrome defined by persistently low CD4 T cell counts (< 300 cells/uL) and characterized by increased prevalence of opportunistic infections, autoimmune clinical manifestations and malignancies. ICL lacks a unifying etiology, and its current standard of care focuses only on preventive and therapeutic antimicrobial strategies. The current trial (ClinicalTrials.gov ID NCT05600920) has been inspired by the pressing clinical need to develop a concomitant host-directed immunological intervention to reduce the risks of severe complications in ICL. IL-7, a potent modulator of thymopoiesis and T cell homeostasis, represents a promising therapeutic target for ICL. The study drug (NT-I7, efineptakin alfa) is a novel homodimeric fusion product of human recombinant IL-7 with a human Fc domain which can induce T cell proliferation, maintaining T-cell responsiveness, along with preventing and reversing T-cell anergy.

Hypothesis: The biological effect of NT-I7 on trafficking, proliferation and apoptosis of T cells may improve the clinical management of ICL, resulting in increased T cell counts in peripheral blood and possible improvement of clinical, radiological or laboratory correlates of prevalent or previously occurring opportunistic infections.

Study Design: This is a single-site, open-label, single-arm, phase 1/2 dose-escalation trial of NT-I7 for ICL, in which we will administer 3 doses of NT-I7 treatment to participants over 24 weeks and follow them for safety and efficacy until week 60. The primary endpoint is the safety of the intervention while secondary and exploratory endpoints will evaluate the trajectory of absolute lymphocyte counts (ALC), CD4, CD8, B and NK cells in peripheral blood as well as possible clinical effects on prevalent chronic opportunistic infections (i.e HPV-related diseases) or on the clinical, radiologic and laboratory sequelae of previous opportunistic infections.

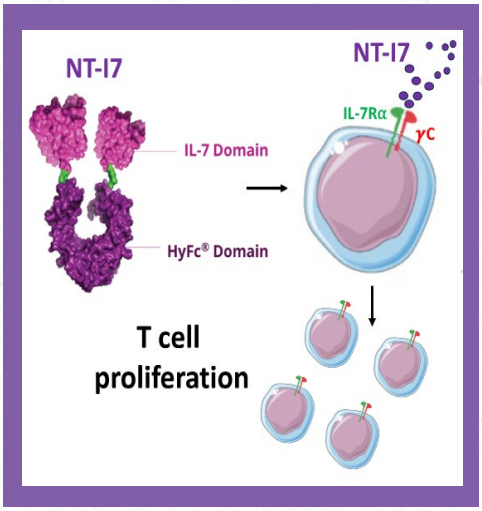

Fig 1. Schematic of the NT-I7 homodimeric fusion product binding to the heterodimeric IL-7Rα-γC receptor on $CD4^+$ T cells to promote cell proliferation. The dosage and administrative schedule for Efineptakin alpha (NT-I7) is shown on the clinicaltrials.gov site with trial ID: NCT 05600920. Trial approved but not yet recruiting.

What we hope to learn: Further characterize the clinical and immunological effects of T cell proliferation, prevention of T cell apoptosis, redistribution/trafficking from peripheral tissue and possible residual thymopoiesis in participants with ICL.

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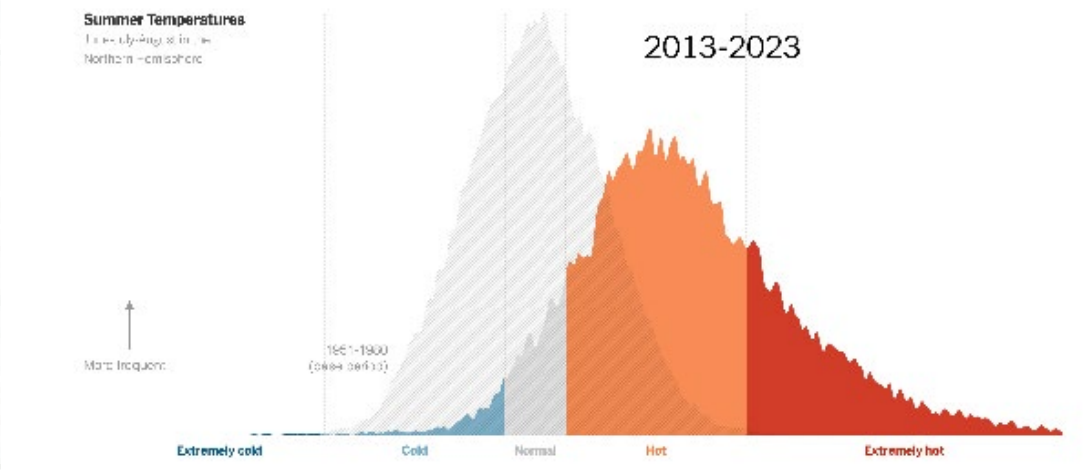
CALL FOR CONTRIBUTORS

IIG call for a "Hot Immunology Summer @ NIH/FDA"



https://www.nytimes.com/interactive/2023/climate/extreme-summer-heat.html

We are launching an initiative to host immunologists during this summer.

Do you have long-standing collaborators that you would like to host over the summer? Do you foresee a manuscript that would benefit from in-person meetings over a week? Are there debates that you would like to resolve with in-person meetings (keeping your immunologist friends close, and your enemies closer)?

The Immunology Interest Group is here to help!

We are launching a call to invite immunologists from across the world to come and collaborate with us over the summer. The IIG will cover their transportation and accommodation (up to one week). In exchange, the invited scientists will present their work and interact with trainees. Note that selected scientists will not be allowed to perform experimental work but will focus on brainstorming with our community. The visits must be completed within this fiscal year (by early September).

Please fill out the survey to nominate outside scientists you would like to host, and answer the queries at:
https://www.surveymonkey.com/r/C3X9VKV

The steering committee of the Immunology Interest Group will review the applications beginning February 19 and select the "hot immunologists" by March 1st, 2024.

Lead Organizers: Mia Sung and Grégoire Altan-Bonnet

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Call for photo submissions for "IIG 2024 retreat" highlight

The IIG annual retreat has been a great success thanks to all the participants and the organizing team led by Grégoire Altan-Bonnet.

We are collecting photo records for a highlight in the next issue. Please reach out to our newsletter editors!

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amy.zhang@nih.gov

Photo credit: Grégoire Altan-Bonnet

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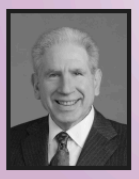
Immunology Interest Group
SEMINAR SERIES

Upcoming seminars

February 2024

February 7, 2024
Julie Blander (Cornell)
Host: Roxane Tussiwand

February 14, 2024
Thirumala-Devi Kanneganti (St Jude)
Host: Christian Mayer



February 21, 2024
Edward A. Fisher (NYU)
Host: P'ng Loke

February 28, 2024
Subash Babu (NIAID/ICER)
Host: Thomas Nutman

March 2024

March 6, 2024
Kathy McCoy (Calgary)
Host: Brian Kelsall

March 13, 2024
Daniel Mucida (Rockefeller)
Host: Chuan Wu

March 20, 2024
Joanne Reed (Garvan)
Host: Susan Moir

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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Join the Listserv!
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

You should recieve a quick confirmation of your subscription, and once you do, you should be able to post.

Please make note of the guidelines for the content that you post.

Sometimes there is a 30 minute delay in recognizing your email, but it is usually recognized quickly, and then you will be able to post.