NIH-FDA IIG

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

NEWSLETTER

MAY 2023

PUBLICATIONS

N-arachidonylglycine is a caloric state-dependent circulating metabolite which regulates human CD4+T cell responsiveness

Meadows AM, Han K, Singh K, Murgia A, McNally BD, West JA, Huffstutler RD, Powell-Wiley TM, Baumer Y, Griffin JL, Sack MN.
iScience. 2023 May 19;26(5).
PMID: 37128607 PMCID: PMC10148119 DOI: 10.1016/j.isci.2023.106578

Fasting interventions blunt innate and adaptive immune orchestrated inflammation. Integrated metabolomic and RNAseq analysis identified a novel fasting-induced circulating metabolite (N-arachidonylglycine), and its cognate CD4+ T cell orphan G-protein coupled receptor. Signaling via this pathway blunted TH1 and TH17 immune responsiveness, identifying how fasting-induced metabolites modulate adaptive immune signaling.

Innate lymphoid cells and innate-like T cells in cancer - at the crossroads of innate and adaptive immunity

Ruf B, Greten TF, Korangy F.
Nature Reviews Cancer. 2023 Apr 20:1-21.
PMID: 37081117 DOI: 10.1038/s41568-023-00562-w

In this Review, we outline hallmarks of innate lymphoid cells (ILCs) and innate-like T cells (ILTCs) and discuss their emerging role in antitumour immunity, as well as the pathophysiological adaptations leading to their pro-tumorigenic function. We also highlight their role in amplifying and complementing conventional T cell functions and summarize immunotherapeutic strategies for targeting ILCs and ILTCs in cancer.

Exploiting docetaxel-induced tumor cell necrosis with tumor targeted delivery of IL-12

Franks SE, Santiago-Sanchez GS, Fabian KP, Solocinski K, Chariou PL, Hamilton DH, Kowalczyk JT, Padget MR, Gameiro SR, Schlom J, Hodge JW.
Cancer Immunology, Immunotherapy. 2023 May 11:1-15.
PMID: 37166485 DOI: 10.1007/s00262-023-03459-7

Employing docetaxel plus NHS-IL-12 combination therapy in MC38 and EMT6 murine models, we observed significant antitumor activity and prolonged survival along with the controlled tumor growth of PD-L1 wild-type and PD-L1 knockout MC38 in vivo. These therapeutic effects provide the rationale to study docetaxel + NHS-IL-12 combination therapy for the design of clinical studies employing this combination or similar combinations of agents in patients who are resistant to checkpoint blockade therapy.

Minimal Antigenic Evolution after a Decade of Norovirus GII.4 Sydney_2012 Circulation in Humans

Parra GI, Tohma K, Ford-Siltz LA, Eguino P, Kendra JA, Pilewski KA, Gao Y.
Journal of Virology. 2023 Feb 28;97(2):e0171622.
PMID: 36688654 PMCID: PMC9973034 DOI: 10.1128/jvi.01716-22

The predominance of GII.4 norovirus, a major cause of gastroenteritis, has been attributed to the continued emergence of variants that escape immune responses to previous infections. Here we showed that the last variant to emerge predominates despite antigenic stability for over 10 years, thus raising questions about the determinants for predominance of noroviruses in the human population.

Cross-reactive neutralizing human monoclonal antibodies mapping to variable antigenic sites on the norovirus major capsid protein

Ford-Siltz LA, Tohma K, Alvarado GS, Kendra JA, Pilewski KA, Crowe Jr JE, Parra GI.
Frontiers in Immunology. 2022;13.
PMID: 36389818 PMCID: PMC9641292 DOI: 10.3389/fimmu.2022.1040836

Norovirus is the major viral cause of acute gastroenteritis worldwide, however, one of the obstacles for the development of therapeutics or preventive vaccines is the extensive genetic and antigenic diversity presented by the virus. In this study, we characterized broadly neutralizing human monoclonal antibodies that map to variable antigenic sites on the capsid of norovirus.

Pyrolyzed deketene curcumin controls regulatory T cell generation and gastric cancer metabolism cooperate with 2-deoxy-d-glucose

MaruYama T, Miyazaki H, Lim YJ, Gu J, Ishikawa M, Yoshida T, Chen W, Owada Y, Shibata H.
Frontiers in immunology. 2023;14.
PMID: 36814928 PMCID: PMC9939626 DOI: 10.3389/fimmu.2023.1049713

In this study, curcumin analog GO-Y022, a food component, was found to inhibited Treg generation in the presence of transforming growth factor beta 1, but showed less impact on Foxp3+ Tregs in the gastric tumor microenvironment. GO-Y022 treatment together with 2-deoxy glucose, a glycolysis inhibitor, was shown to correct gastric tumor metabolisms, inhibit tumor cell survival and promote anti-tumor immunity.

HLA class I signal peptide polymorphism determines the level of CD94/NKG2-HLA-E-mediated regulation of effector cell responses

Lin Z, Bashirova AA, Viard M, Garner L, Quastel M, Beiersdorfer M, Kasprzak WK, Akdag M, Yuki Y, Ojeda P, Das S, Andresson T, Naranbhai V, Horowitz A, McMichael AJ, Hoelzemer A, Gillespie GM, Garcia-Beltran WF, Carrington M.
Nat Immunol. 2023 Jun 1. doi: 10.1038/s41590-023-01523-z. Epub ahead of print.
PMID: 37264229 DOI: 10.1038/s41590-023-01523-z

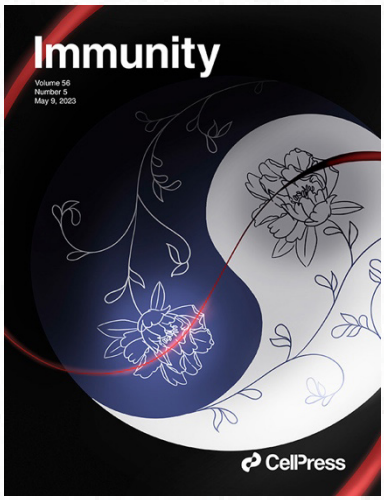
HLA-E binds epitopes derived from HLA-A, -B, -C, -G signal peptides and serves as a ligand for CD94/NKG2 receptors expressed on subsets of effector cells. The impact of HLA signal peptide polymorphism on HLA-E cell surface expression and subsequent CD94/NKG2 recognition was systematically quantitated, facilitating development of metrics to measure the influence of CD94/NKG2-HLA-E interactions in human disease.

Restraint of IFN-gamma expression through a distal silencer CNS-28 for tissue homeostasis

Cui K, Chen Z, Cao Y, Liu S, Ren G, Hu G, Fang D, Wei D, Liu C, Zhu J, Wu C, Zhao K.
Immunity. 2023 May 9;56(5):944-58
PMID: 37040761 PMCID: PMC10175192 DOI: 10.1016/j.immuni.2023.03.006

There are multiple enhancer regions for the Ifng locus, but Ifng restraint is unknown. We identified a silencer CNS–28 that diminishes enhancer-promoter interactions within Ifng locus. Together with other regulatory elements, CNS–28 activity ensures immune cell quiescence and minimizes autoimmunity.

This work is also the cover story of Immunity (Volume 56, Issue 5):



On the cover: In this issue, Cui, Chen, Cao, Liu et al. (pages 944–958) report the identification of a negative regulatory element (CNS–28) that restrains IFN expression to ensure tissue homeostasis. CNS–28 forms a local 3D domain with two other regulatory elements, CNS–22 and CNS–34, in a manner dependent on the transcription factors MLL4 and GATA3; this structure prevents activation of Ifng transcription by the CNS–22 enhancer. The positive and negative mechanisms regulating expression of IFNg is depicted by the Taiji figure. Ifng genomic DNA (red ribbon) is embedded within repressive 3D chromatin (Yin; flower in the dark side) and activating 3D chromatin (Yang; flower in the light side). Illustration by Qinglan Emily Yu at the Bryn Mawr School.

Continued>>

Congratulations to NIH IIG Members Elected to the American Academy of Arts and Sciences in 2023

Since its founding in 1780, the American Academy of Arts and Sciences has celebrated outstanding achievement in a variety of disciplines from the humanities and arts to math, physics, and biology. The Academy's members, who are leaders in their fields, work together and with other experts "to cultivate every art and science which may tend to advance the interest, honor, dignity, and happiness of a free, independent, and virtuous people." The Academy also conducts independent, multidiscplinary, non-partisan research across multiple areas of inquiry to address the complex problems facing the modern world.

Ronald N. Germain, NIH National Institute of Allergy and Infectious Diseases
Andre Nussenzweig, NIH National Cancer Institute

Congratulations to NIH IIG Members Elected to the National Academy of Sciences in 2023

The National Academies provide expert advice to the U.S. government on issues of science, health, and engineering and, today, comprise three private, nonprofit institutions: The National Academy of Sciences (NAS), National Academy of Engineering (NAE), and National Academy of Medicine (NAM). The NAS is the oldest of these, established by the U.S. Congress in 1863. Membership to the Academies is considered one of the highest honors bestowed to a U.S. scientist.

Andre Nussenzweig, NIH National Cancer Institute
John J. O'Shea, NIH National Institute of Arthritis and Musculoskeletal and Skin Diseases

Congratulations to NIH IIG Members Elected to the Association of American Physicians in 2023

The Association of American Physicians (AAP) is an honorary medical society founded in 1885 by the Canadian physician Sir William Osler and six other distinguished physicians of his era for "the advancement of scientific and practical medicine." Election to the AAP is an honor extended to physicians with outstanding credentials in basic or translational biomedical research and is limited to 70 persons per year. The overarching goals of the AAP include the promotion of professional and social interaction among biomedical scientists, the dissemination of important information related to biomedical science and teaching, the recognition of outstanding, diverse physician-scientists through membership, and the establishment of role models to kindle new generations of high achievers in medicine and medical science.

Richard Childs, NIH National Heart, Lung, and Blood Institute
Luigi Notarangelo, NIH National Institute of Allergy and Infectious Diseases
Michael Sack, NIH National Heart, Lung, and Blood Institute
Naomi Taylor, NIH National Cancer Institute

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IIG-FAES Symposia: Barrier Immunity

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

The IIG committee are excited to share the program and lineup of the upcoming Barrier Immunity symposium that will take place in November 2023.

WEDNESDAY, NOVEMBER 15

The Epithelial Barrier

- **Sunny Shin** (U Penn)
- **De'Broski Herbert** (U Penn)
- **Niki Moutsopolous** (NIDCR)
- Short Talk from Abstracts

Inflammation and myeloid cells

- **Kate Fitzgerald** (U Mass)
- **Renato Ostuni** (Vita-Salute San Raffaele)
- **John O' Shea** (NIAMS)
- Short Talk from Abstracts

Poster Session 1

Workshop 1

- Short Talks from Abstracts

Adaptive Immunity at the barrier

- **Lydia Lynch** (Harvard)
- **Jenny Ting** (UNC)
- **Michael Lenardo** (NIAID)
- Short Talk from Abstracts

THURSDAY, NOVEMBER 16

Pathobionts at the barrier

- **Christina Stallings** (Wash U)
- **Richard Maizels** (U Edinburgh)
- **Yasmine Belkaid** (NIAID)
- Short Talk from Abstracts

Viral Immunity at the barrier

- **Clive McKimmie** (U Leeds)
- **Carolyn Coyne** (Duke)
- **Gabriel Parra** (CBER)
- Short Talk from Abstracts

Poster Session 2

Workshop 2

- Short Talks from Abstracts

Neuro-Immune Axis at the barrier

- **Mauro Costa-Mattioli** (BCM)
- **Gloria Choi** (MIT)
- **Vanja Lazaveric** (NCI)
- Short Talk from Abstracts

FRIDAY, NOVEMBER 17

Systems Immunology at the barrier

- **Sepideh Dolatshahi** (U Virginia)
- **Smita Krishnaswamy** (Yale)
- **Ron Germain** (NIAID)
- Short Talk from Abstracts

Tumor Immunity at the barrier

- **TBD**
- **Edna Cukierman** (Fox Chase)
- **Giorgio Trinchieri** (NCI)
- Short Talk from Abstracts

The background is a vertical cross sectional view of confocal microscopic images showing intestinal epithelium grown on-chip (Credit: Wyss Institute at Harvard University; PMID: 29440725)

Continued>>

Immunology Interest Group

SPOTLIGHT

Dr. Jin is a Tenure-Track Investigator and Chief of the Neuro-Immune Crosstalk Unit in the National Institute of Allergy and Infectious Diseases. To learn more about his work visit: https://www.niaid.nih.gov/research/hao-jin-phd

Hao Jin, Ph.D.

Tell us about your science.

My research lies at the intersection of neuroscience and immunology, with the goal of decoding how multidimensional neuro-immune interactions regulate immune responses. One focus is to understand how the body-brain axis enables the brain to monitor and regulate immune responses. We are combining multiomics, functional imaging, targeted manipulation, and circuit cracking to decipher the cells, circuits and logic for immune sensing and regulation by the bidirectional body-brain 'highway'.

I am also interested to know how the brain imposes the modification of immune responses in response to external stimuli and internal states. We are actively investigating how sensory cues predicting the upcoming threat or infection, can impact the immune system to forge either a beneficial or pathological response. I hope that my research will start to expose the functional roles of numerous neuro-immune connections that have been described anatomically for years, and in a broader term, serves as a distinctive window to peek into the workings of the control of body physiology by the brain. Ultimately my larger dream is to translate the findings of our research into meaningful strategies that harness the therapeutic power of the nervous system to regulate immune functions in various immune-related diseases.

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

When I was doing a rotation in my graduate school, I joined a lab that studies immune cells and blood stem cells using zebrafish as a model organism. The optical transparency of fish embryos allowed me to observe immune cells marked with fluorescent reporters in real time, within the context of intact animals under microscopy. Numerous fascinating behaviors unfolded before my eyes from the patrol of these cells in tissues as sentinels under steady states, to the rapid and orderly mobilization of them in response to infections and the timely resolution after the infections were cleared. I was immediately hooked and decided to continue my PhD study in that lab. Looking back, if my first experiment had been a complex multiparameter flow cytometry experiment which I don't mean to undermine the power of, my path would have been very different.

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

When I began college, I had a broad focus on mathematics, physics and computer science. In my sophomore year, I took an elective course of introductory biology and it was there that I was first exposed to the appeal of biology. The professor's stimulating and engaging teaching decomposed complicated biological concepts through a blend of historical reflection, technical perspective and tangible examples. This experience is instrumental in sparking my interest in biology and as a result, I switched my major to biology. I am genuinely grateful to that professor and aspire to bring similar positive experiences to other people through my research and mentorship.

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

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

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

The collaborative vibe ingrained in the community. The community comprises a diverse group of researchers with a wide range of perspectives and areas of expertise, spanning from technique development and immune regulation to disease models and clinical studies. It's probably fair to say, whenever you need help in an unknown area, you can always find someone within the community who has the matching expertise to help. Moreover, the structure and funding system of NIH-FDA, featuring relatively small lab size and exemption from grant writing naturally bond different labs together to catalyze the collaboration toward a bigger common goal that individual labs could not achieve alone. I believe that this collaboration is key to advancing our understanding of immunology and developing new treatments.

How do you spend your free time?

I have loved swimming since I was very young and still try to do it whenever possible. I also enjoy reading, especially detective and historical fiction, in my free time.

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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.

Selective TCR-targeting with a bifunctional Ab-fusion molecule for unresectable solid tumors
PI: James L. Gulley, M.D. – Acting Clinical Director and Co-Director center for Immuno-Oncology, NCI, DIR.

Background: Clinical success of treating solid tumors using Immunotherapy is not uniformerly successful and efficacy is reduced further in unresectable, locally advanced or metastatic solid tumors. Novel strategies to enhance tumor infiltrating lymphocytes (TILs) to advance solid tumor immuno-oncological (IO) efficacy are being pursued. STAR0602 is a novel bifunctional antibody-fusion molecule that selectively activates and expands a subset of human αβ T cells expressing variable (V) b6 and b10 regions of the T cell receptor (TCR). It works by simultaneously engaging a novel, non-clonal mode of TCR activation with cytokine (IL-2) co-stimulation. STAR0602 selectively targets a common subset of T cells found to be enriched in the TILs of tumors biopsies and activates the endogenous TCR outside of the TCR-MHC binding pocket. This allows for potent anti-tumor activity through a PD-1 independent mechanism and leads to a new IO category of selective T cell activators.

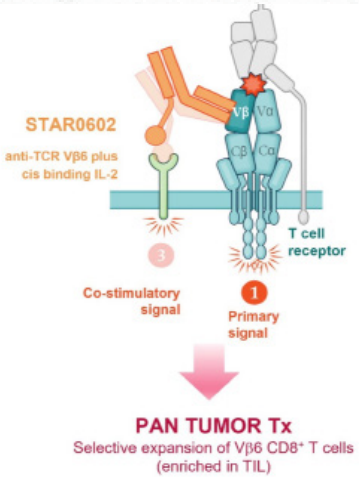

Fig 1. Schematic of the STAR0602 bifunctional anti-body fusion molecular binding to both the TCR and IL-2 receptors on a subset of αβ TILs to increase cytotoxic activity independent of checkpoint inhibition.

Hypothesis: STAR0602, via it novel effect on promoting TIL activation, will be a safe and effective novel agent to reduce tumor mass and improve the prognosis in patients with advanced solid tumor with otherwise limited treament options.

Study Design: Clinical trial NCT05592626, Protocol 001099-C, is an open-label, multicenter, phase 1/2 study to evaluate the safety, tolerability, and preliminary clinical activity of STAR0602 as a single agent in patients with advanced solid tumors.
The phase 1 dose-escalation stage of the trial is being conducted in patients with virally associated malignancies, or malignancies harboring either a high tumor mutational burden or microsatellite instability, who have failed standard therapies or for whom no standard therapies exist. The primary endpoint of the trial is to determine the safety and tolerability of STAR0602, as measured by the incidence and severity of adverse events. Secondary and exploratory endpoints include the preliminary clinical activity of STAR0602, as measured by objective response rate (ORR), duration of response (DOR), progression-free survival (PFS), and overall survival (OS).

What we hope to learn: The trial is ongoing, and the first patient has been dosed with STAR0602. The study aims to provide valuable insights into the safety and efficacy of STAR0602 as a potential treatment option for patients with advanced solid tumors.

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Immunology Interest Group
SEMINAR SERIES

Upcoming seminars

Missed a seminar?

Catch up on prior talks at...

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

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

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

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Immunology Interest Group

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

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