NIH-FDA IIG

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

NEWSLETTER

AUGUST 2022

PUBLICATIONS

Novel GLCCI1-BRAF fusion drives kinase signaling in a case of pheochromocytomatosis

Green BL, Grant RRC, Richie CT, Chatterjee B, Sampaio De Melo M, Barr FG, Pacak K, Agarwal SK, Nilubol N
Eur J Endocrinol. 2022 Jul 01; 187(1) 185-196
DOI: 10.1530/EJE-21-0797, PMID: 35861986

A patient with recurrent functional pheochromocytoma (pheochromocytomatosis) underwent resection of the recurrence at the NIH clinical center. Next-generation sequencing identified a BRAF fusion oncogene with the 5' end disrupted by the GLCCI1, a novel and potentially targetable fusion. Transfection of GLCCI1-BRAF caused upregulation of MAPK pathway signaling and EMT markers in vitro.

Long-term antibiotic exposure promotes mortality after systemic fungal infection by driving lymphocyte dysfunction and systemic escape of commensal bacteria

Drummond RA, Desai JV, Ricotta EE, Swamydas M, Deming C, Conlan S, Quinones M, Matei-Rascu V, Sherif L, Lecky D, Lee CR, Green NM, Collins N, Zelazny AM, Prevots DR, Bending D, Withers D, Belkaid Y, Segre JA, Lionakis MS.
Cell Host Microbe. 2022 May 07
DOI: 10.1016/j.chom.2022.04.013, PMID: 35568028, PMCID: PMC9283303

In this work, it was shown that antibiotics damage IL-17- and GM-CSF-dependent lymphocyte responses in the gut which subsequently impair local antifungal immune responses, leading to uncontrolled fungal infection in the intestine, non-inflammatory escape of commensal bacteria, and systemic bacterial co-infection. This work provides a mechanistic explanation for why antibiotic use is linked with an increased risk of invasive fungal infections in humans and highlights the need for antibiotic stewardship.

Highly active CAR T cells that bind to a juxtamembrane region of mesothelin and are not blocked by shed mesothelin

Liu X, Onda M, Watson N, Hassan R, Ho M, Bera TK, Wei J, Chakraborty A, Beers R, Zhou Q, Shajahan A, Azadi P, Zhan J, Xia D, Pastan I. .
Proc Natl Acad Sci U S A. 2022 May 10;119(19):e2202439119.
DOI: 10.1073/pnas.2202439119. Epub 2022 May 5. PMID: 35512094

Mesothelin (MSLN) is a cell-surface protein that is a popular target for antibody-based therapies. We have identified shed MSLN as a major obstacle to successful antibody therapies and prepared a monoclonal antibody that inhibits shedding and makes very active CAR T cells whose activity is not blocked by shed MSLN.

Double negative T regulatory cells: an emerging paradigm shift in reproductive immune tolerance?

Bafor EE, Valencia JC, Young HA
Front Immunol. 2022 Jul 01; 13 886645
DOI: 10.3389/fimmu.2022.886645, PMID: 35844500, PMCID: PMC9283768

This extensive review describes the phenotype, function and plasticity of the unique double negative T regulatory cells (DNTregs) and their role in immune tolerance. This review also compares DNTregs to conventional CD4+Tregs and identifies unique similarities and differences between these cells and as relates to female reproductive immune tolerance.

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Reduction of Influenza A Virus Transmission in Mice by a Universal Intranasal Vaccine Candidate is Long-Lasting and Does Not Require Antibodies

Graeme E Price, Chia-Yun Lo, Julia A Misplon, Suzanne L Epstein

J Virol. 2022 Jun 22; 96(12) e0032022
DOI: 10.1128/jvi.00320-22, PMID: 35638848, PMCID: PMC9215256

Despite allowing low-level infection, intranasal immunization with adenovirus vectors expressing the conserved antigens influenza nucleoprotein and matrix 2 reduces influenza virus transmission from vaccinated to unvaccinated contact mice. Here, we show that antibodies are not required for this transmission reduction, suggesting a role for T cells. We also show that transmission blocking could be achieved in recipients of different ages and remained effective for at least a year following a single-dose vaccination.

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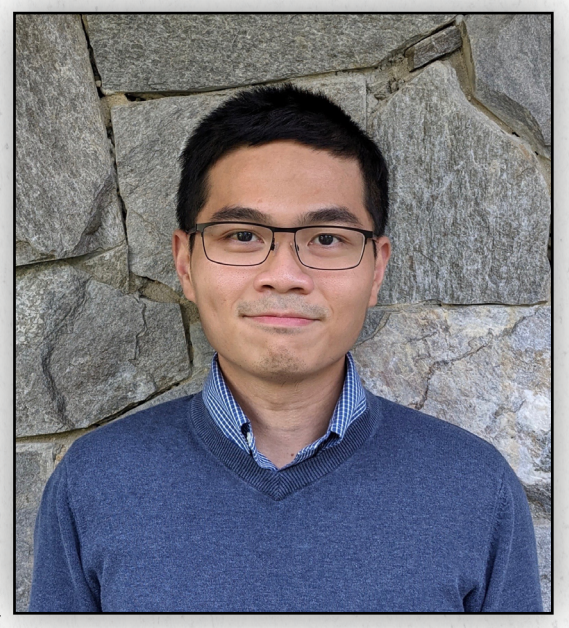
Immunology Interest Group

SPOTLIGHT

Dr. Tan is a Stadtman Investigator in the Laboratory of Immunogenetics and is Chief of the Antibody Biology Unit at NIAIDI. To learn more about his work visit: https://www.niaid.nih.gov/research/joshua-tan-phd

Tell us about your science.

My research investigates the human antibody response to infectious pathogens at the single B cell level through the isolation and characterization of monoclonal antibodies. Our two major goals are to study the biology of the humoral response to vaccination and infection, and to investigate the use of monoclonal antibodies to prevent infection or as tools for vaccine design. We're currently studying the antibody response to SARS-CoV-2, Plasmodium falciparum and Mycobacterium tuberculosis, which all cause diseases with high global impact.



Joshua Tan, Ph.D.

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

I've been interested in science since childhood, and I wanted to work in a field that is directly linked to combating infectious disease. My journey in immunology started during my PhD in Oxford – at the start of the program we were given the opportunity to perform rotations at different labs. During one of the briefing sessions, I heard a talk about rare individuals living in malaria-endemic areas who made cross-reactive antibodies to P. falciparum-infected erythrocytes. I was hooked from that moment and spent my PhD trying to find these antibodies and have not looked back since.

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

I've had amazing mentors who have shaped my career trajectory in a major way. Apart from good advice on science and leading a research group, one of the biggest ways they have helped me has been by giving me opportunities to present my work and connecting me to leading researchers in the field, some of whom have become great collaborators over the years.

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

In relation to my research field, I think we'll see big advancements in antibody engineering. We're just scratching the surface as to how we can modify antibodies to improve potency, and I think we'll see great progress in this area in the near future, especially with the advancement of structural analysis through systems like AlphaFold.

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

I very much appreciate the spirit of collaboration that exists within the NIH-FDA Immunology community. I have great collaborations with a number of groups within this community, and their generosity and willingness to work together on projects has really helped me as a tenure-track investigator.

How do you spend your free time?

I enjoy reading, playing board games and hiking.

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2022 IIG Workshop

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

The 2022 FDA-NIH IIG Workship planning is underway!

Registration for the IIG Workshop on December 8 – 9, 2022 (Natcher Conference Center) will open on August 26, 2022.

Registration will close when all spaces are filled or on September 29, 2022, whichever comes first. So while you're enjoying your summer, also start planning your abstract submission!

Natcher Conference Center (Building 45), National Institutes of Health (NIH)

As of now, we expect this to be a hybrid meeting, with space for ~200 people in-person and the remainder as virtual only.

You may specify your preference of attendance option during registration. However, in the case of oversubscription for in-person attendance, preference for the in-person option will be given to those submitting abstracts for presentations. As in the past, some abstracts will be selected for short talks and the rest will be considered for in-person poster presentations at Natcher. Posters will also be available on-line as static presentations (but will not be interactive). We'll update all plans if conditions dictate a change to an all-virtual format.

Our gurus for the workshop will be Erika Pearce, from Johns Hopkins University, and NIAID's own Yasmine Belkaid. We hope that journal editors will again be our guests, and planning for special sessions (over and above the science driven by your great data) is underway as well. So, get ready!

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Congratulations to the 2022 NIH-UPenn Scholars!

The NIH-Penn Immunology Graduate Partnership Program welcomes the 2022 Class of Advanced Scholar in Immunology. Initiated in 2001, the NIH-Penn Immunology Graduate Partnership a unique inter-campus collaboration providing access to research resources and mentorship at both centers to train the next generation of innovative scientists. Students can conduct basic, translation and clinical research within intramural laboratories.

The new class will start their academic year on August 30th at the University of Pennsylvania under the leadership of Vanja Lazarevic, PhD, Program Director. Special acknowledgement goes to Tom Misteli, Mike Lenardo, and Steve Holland for their leadership and support of this program and its mission.

Tim Johnston
B.S.

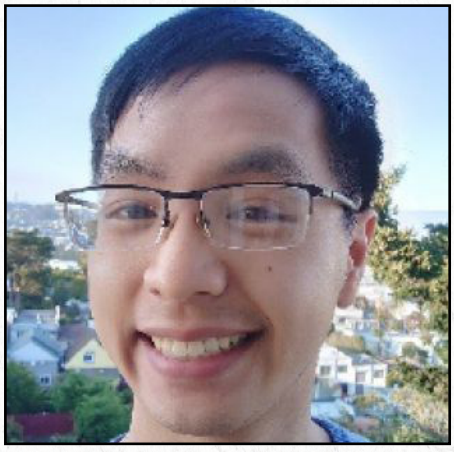
Biology
University of Minnesota

Ivanna Molina-Lopez
B.S.

Microbiology
University of Puerto Rico - Humacao

Harrison Wang
B.S.

Physics & Biology
UCSD



Simon Zhou
B.S.

Molecular, Cell & Developmental Biology
UC Santa Cruz

Read more about Tim, Ivanna, Harrison, and Simon at:
https://www.med.upenn.edu/nih-igg-partnership/students.html

To learn more about the NIH-Penn Immunology Graduate Partnership Program, visit:
https://www.med.upenn.edu/nih-igg-partnership/

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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.

Pilot Study to Evaluate the Effect of Nicotinamide Riboside on Immune Activation in Psoriasis

PI: Michael N. Sack, MD, Ph.D. – Laboratory of Mitochondrial Biology and Metabolism, NHLBI DIR.

Background related to the study:

The concept that boosting intracellular NAD+ levels is gaining interest as an intervention to blunt inflammation via immunometabolic regulation. The vitamin B3 analogue, nicotinamide riboside (NR), is a precursor of intracellular NAD+ restoration. Interestingly, NR supplementation in aging and Parkinson disease blunts serum and cerebrospinal fluid inflammatory cytokine levels respectively, although the direct mechanisms remain elusive. In our laboratory we have previously shown that NR blunts the NLRP3 inflammasome and type I interferon in human healthy subjects and in systemic lupus erythematosus monocytes, via modulating mitochondrial fidelity and inosine metabolism respectively.1, 2

A question arose whether this biology is operational in the adaptive immune system. To explore this, we began studying the role of NR on primary CD4+ T cells extracted from healthy volunteers and matched patients with psoriasis. In this ex-vivo study we find that NR blunts T cell receptor mediated secretion of IL-17 (Fig. 1) and are exploring the underlying metabolic and molecular mechanisms. To expand our understanding of this we designed a pilot blinded placebo-controlled NR-supplemented clinical study to explore this biology in human subjects with this Th17-linked inflammatory disease. Recruitment is ongoing and samples are being collected for genome and metabolome profiling and to explore potential effects on chromatin remodeling.

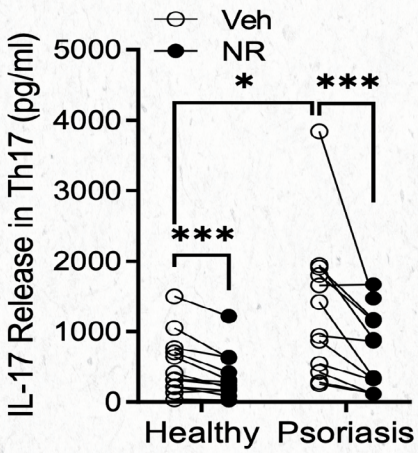

Fig 1. IL-17 release in Th17 differentiated CD4+ T cells isolated from Psoriatic and healthy subjects (n=12/group). CD4+ T cells was differentiated with 0.5 mM NR and 10% autologous serum for 3 days by αCD3 and αCD28. Veh - Vehicle.

Expectations of what we may learn from this trial?

Prior clinical studies using NR have not directly evaluated the effect of this NAD+-boosting strategy in human subjects with an active inflammatory disease. This clinical intervention study will augment the strength of our ex-vivofindings and will demonstrate whether this nutritional intervention has merit to explore further in this prevalent inflammatory disease.

References:

1. Traba J, Kwarteng-Siaw M, Okoli TC, Li J, Huffstutler RD, Bray A, Waclawiw MA, Han K, Pelletier M, Sauve AA, Siegel RM and Sack MN. Fasting and refeeding differentially regulate NLRP3 inflammasome activation in human subjects. The Journal of clinical investigation. 2015;125:4592-600.

2. Wu J, Singh K, Lin A, Meadows AM, Wu K, Shing V, Bley M, Hassanzadeh S, Huffstutler RD, Schmidt MS, Blanco LP, Tian R, Brenner C, Pirooznia M, Kaplan MJ and Sack MN. Boosting NAD+ blunts TLR4-induced type I IFN in control and systemic lupus erythematosus monocytes. The Journal of clinical investigation. 2022;132.

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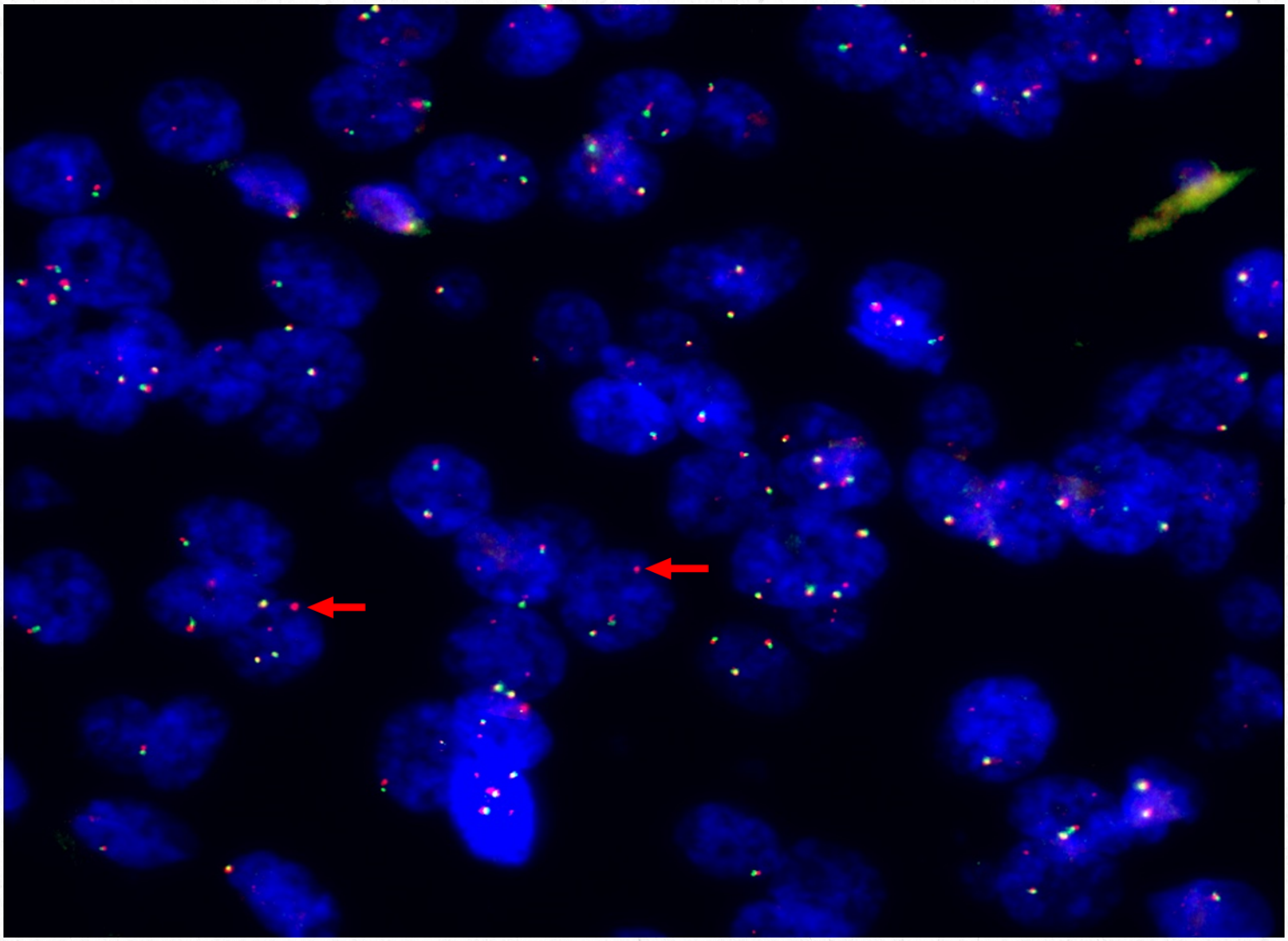
BRAF break-apart assay of recurrent pheochromocytoma containing novel GLCCI1-BRAF fusion



BRAF break-apart assay of recurrent pheochromocytoma containing novel GLCCI1-BRAF fusion
FISH assay confirming BRAF gene rearrangement. The break-apart assay was positive for an isolated BRAF 3' signal in 46% of the analyzed nuclei (criterion for positive ≥9%). Probes: BRAF 5' end – green, BRAF 3' end – red (indicated by red arrows).

Image credit:
Benjamin Green, MD
Surgical Oncology Program
National Cancer Institute
National Institutes of Health

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Join the IIG Steering Committee!

We are seeking nominations of dedicated, energetic members of the immunology community to serve on the Immunology Interest Group (IIG) Steering Committee! The deadline for nomications is Augsust 5th.

The IIG Steering Committee is a group of enthusiastic individuals responsible for organizing the weekly IIG seminar series, the annual Immunology Workshop and the new IIG newsletter. Only through your willingness to volunteer can the IIG remain a vibrant and beneficial organization.

We are seeking nominations for immunologists in the following four categories:

- Tenured PI (2 year term; 2 positions available)
- Tenure-track Investigator / Assistant Clinical Investigator (2 year term; 2 positions available)
- Staff Scientist / Staff Clinician (2 year term; 2 positions available)
- Postdoctoral Fellow / Graduate Student (1 year term; 4 positions available)

*Note: Trainee members must be available from October 2022-October 2023.

To foster an open and inclusive environment, the IIG steering committee would like to solicit nominations from all sectors and demographics within the IIG community. Allowing diverse voices and perspectives will help strengthen the IIG's goals and directions.

Please feel free to nominate yourself or others.

To submit nominations, please visit:
https://forms.office.com/g/kZQQnczUtt

For multiple nominations please select the option 'submit another response' after submitting your nomination.

If you cannot access Microsoft Forms, email parkhurm@mail.nih.gov with the following information about the nominee(s): name, position (see above), institute, email address, confirmation they will run for election if selected, if previously served on the IIG committee, and a brief explanation why you have nominated this individual.

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Immunology Interest Group
SEMINAR SERIES

We hoped that you enjoyed the seminar speakers from the 2021-2022 season!

In case you missed a seminar this past year and want to catch-up over the summer hiatus, please remember that you can find links to many of the recordings on this IIG website: https://www.niaid.nih.gov/research/immunology-seminars

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

The IIG 2022-2023 seriminar series season will start on Sept. 7th 2022 with the Tom Waldman Symposium. With a series fo exellent speaker throughout the year!

Stay tuned for updates and announcments!

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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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