

NIH-FDA IIG

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

NEWSLETTER

NOVEMBER 2022

PUBLICATIONS

Dying of Stress: Chemotherapy, Radiotherapy, and Small-Molecule Inhibitors in Immunogenic Cell Death and Immunogenic Modulation

Fabian KP, Kowalczyk JT, Reynolds ST, Hodge JW

Cells. 2022 Nov 29; 11(23) 3826

DOI: 10.3390/cells11233826

This review discusses the mechanisms of immunogenic cell death and immunogenic modulation and their relevance in the anti-tumor activity of radiotherapies, chemotherapies, and small-molecule inhibitors. More detailed investigation on the collaboration of immunogenic cell stress with immunotherapy will contribute to improving

Tipping the scales: Immunotherapeutic strategies that disrupt immunosuppression and promote immune activation

Santiago-Sánchez GS, Hodge JW, Fabian KP

Front Immunol. 2022 Sep 08; 13 993624

DOI: 10.3389/fimmu.2022.993624, PMID: 36159809, PMCID:

PMC9492957

This review aims to provide an overview of select therapeutic strategies that tip the balance from immunosuppression to immune activity in the tumor microenvironment. A deeper understanding of the known immunosuppressive pathways, as well as identifying new ones, could enable the development of immunotherapies relevant to many cancers.

Cholesterol Binds the Amphipathic Helix of IFITM3 and Regulates Antiviral Activity

Rahman K, Datta SAK, Beaven AH, Jolley AA, Sodt AJ, Compton AA

J Mol Biol. 2022 Oct 15; 434(19) 167759

DOI: 10.1016/j.jmb.2022.167759, PMID: 35872070, PMCID: PMC9342930

We describe the cell-intrinsic antiviral protein IFITM3 as a cholesterol binding protein. Single mutations that disrupt an amphipathic alpha helix in IFITM3 result in loss of cholesterol binding and loss of antiviral activity against Influenza A virus.

Loss of CD47 alters CD8+ T cell activation in vitro and immunodynamics in mice

Nath PR, Pal-Nath D, Kaur S, Gangaplara A, Meyer TJ, Cam MC, Roberts DD

Oncoimmunology. 2022 Sep 06; 11(1) 2111909

DOI: 10.1080/2162402X.2022.2111909, PMID: 36105746,

PMCID: PMC9467551

Previous studies have established that therapeutic blockade of CD47 enhances innate and adaptive antitumor immunity. However, this paper demonstrates that complete loss of CD47 in the tumor microenvironment results in loss of CD8 T cells with effector phenotypes and increased apoptotic cell death.

Continued>>

Quantification of Neutrophils Undergoing NET Formation and Distinguishing Mechanisms of Neutrophil Cell Death by Use of a High-Throughput Method

Nakabo S, Kaplan MJ, Gupta S

Methods Mol Biol. 2022; 2543 129-140

DOI: 10.1007/978-1-0716-2553-8_11, PMID: 36087264

Here we describe an automated high-throughput method to quantify NETting neutrophils in real time using a two-color, live-content imaging platform, the IncuCyte™S3 (Essen BioScience, Inc.) system, coupled to membrane integrity-dependent dual-dye approach to image intracellular and extracellular DNA. This platform can help to assess neutrophil physiology and to develop and test therapeutic targets.

Immune targeting of three independent suppressive pathways (TIGIT, PD-L1, TGF) provides significant antitumor efficacy in immune checkpoint resistant models

Franks SE, Fabian KP, Santiago-Sánchez G, Wolfson B, Hodge JW

Oncoimmunology. 2022 Oct 01; 11(1) 2124666

DOI: 10.1080/2162402X.2022.2124666, PMID: 36211806,

PMCID: PMC9542338

We report for the first-time anti-TIGIT in combination with bintrafusp alfa results in prominent antitumor activity and increase in overall survival in the MC38-CEA colon carcinoma and the TC1, HPV+ lung carcinoma models. These data represent potential indicators of response or resistance to therapy that could be monitored in patients enrolled in clinical trials.

In Vivo Generation of SSA/Ro Antigen-Specific Regulatory T Cells Improves Experimental Sjögren's Syndrome in Mice

Xu J, Liu O, Wang D, Wang F, Zhang D, Jin W, Cain A, Bynum A, Liu N, Han Y, Chen W

Arthritis Rheumatol. 2022 May 23

DOI: 10.1002/art.42244, PMID: 35606923

Sjögren's syndrome (SS) is a systemic autoimmune disease, and T cells play an important role in the initiation and perpetuation of the disease. In this study, we show that the combination of anti-CD4 mAb with autoantigen-specific peptide Ro480 generated SSA/Ro antigen-specific Treg cells in vivo, which suppress experimental SS in mice and maintain the function of salivary glands.

Opposing functions of circadian protein DBP and atypical E2F family E2F8 in anti-tumor Th9 cell differentiation

Park SA, Lim YJ, Ku WL, Zhang D, Cui K, Tang LY, Chia C, Zanvit P, Chen Z, Jin W, Wang D, Xu J, Liu O, Wang F, Cain A, Guo N, Nakatsukasa H, Wu C, Zhang YE, Zhao K, Chen W

Nat Commun. 2022 Oct 14; 13(1) 6069

DOI: 10.1038/s41467-022-33733-8, PMID: 36241625, PMCID: PMC9568563

In this study, we discovered that TGF- and IL-4 signaling-mediated phosphorylation of the serine 213 site in the linker region of the Smad3 (pSmad3L-Ser213) rather than the C-terminal of Smad3 (pSmad3C) is necessary and sufficient for Il9 gene transcription and thus Th9 differentiation. We further identify DBP and E2F8 as an activator and repressor, respectively, for Il9 transcription by pSmad3L-Ser213, which regulate Th9 mediated anti-tumor immunity in mice.

Exploring the immunomodulatory role of virtual memory CD8+ T cells: Role of IFN gamma in tumor growth control

Savid-Frontera C, Viano ME, Baez NS, Lidon NL, Fontaine Q, Young HA, Vimeux L, Donnadieu E, Rodriguez-Galan MC

Front Immunol. 2022 Oct 18; 13 971001

DOI: 10.3389/fimmu.2022.971001, PMID: 36330506, PMCID: PMC9623162

In this work we show that systemic expression of IL-12 plus IL-18 induced an alteration in the normal TVM vs TMEM/TEFF distribution in secondary lymphoid organs and a preferential enrichment of TVM cells in the melanoma (B16) and the pancreatic ductal adenocarcinoma (KPC) tumor models. Using our KPC bearing OT-I mouse model, we observed a significant increase in CD8+ T cell infiltrating the tumor islets after IL-12+IL-18 stimulation with a lower average speed when compared to those from control mice. Thus, our studies provide significant new information that indicates an important role of TVM cells in the immune response against cancer.

Rapalogs downmodulate intrinsic immunity and promote cell entry of SARS-CoV-2

Shi G, Chiramel AI, Li T, Lai KK, Kenney AD, Zani A, Eddy AC, Majdoul S, Zhang L, Dempsey T, Beare PA, Kar S, Yewdell JW, Best SM, Yount JS, Compton AA

J Clin Invest. 2022 Oct 20

DOI: 10.1172/JCI160766, PMID: 36264642

We describe how FDA-approved mTOR inhibitors suppress cell-intrinsic immunity and increase cellular susceptibility to multiple virus infections, including SARS-CoV-2. Furthermore, administration of rapamycin to hamsters/mice increases COVID-19 severity in vivo.

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SPOTLIGHT

Dr. Sadtler is an Earl Stadtman Tenure-Track Investigator and Chief of the Section on Immunoengineering in the National Institute of Biomedical Imaging and Bioengineering. To learn more about her work visit:

<https://irp.nih.gov/pi/kaitlyn-sadtler>

Tell us about your science.

Our lab works at the intersection of immunology and regenerative medicine, specifically looking at traumatic muscle injury. We use a combination of approaches focused on understanding the basic immunologic mechanisms behind responses to biomaterial scaffolds used in regenerative medicine and how we can modulate those to promote functional tissue repair.

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

In general, science is a giant puzzle and when the pieces fit it's one of the most satisfying feelings. The moment of knowing something, however large the fact, before anyone else is thrilling. Immunology specifically is just a fascinating system that touches almost all processes in the human body. Regenerative medicine has a hint of science fiction that is just fun to work on.

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

When I was a postbac, I had an experience where I was told directly and bluntly that laboratory science should be reserved for men. I remember standing on the steps of Building 4 thinking about quitting research and just not sure what to do next. I wound up being moved to another group and working with Dr. Rajat Varma. He truly saved my career, showing me the kind of PI that I wanted to be in a lab that supported teamwork and balance. I am forever thankful for his mentorship and kindness.

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

I think that the field of wound care and tissue engineering has hit a surge in new findings while integrating immunologic principles and believe that materials to diminish scarring, promote tissue repair, and improving cosmetics will see more translation to the clinic. Medical device implants that replace the function of missing or damaged organs are also benefiting from this research and those continue to make leaps and bounds in integration within the human body.

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

Finding new mentors has been a fantastic experience in the immunology community, and spreading the word about bioengineering and getting in touch with immunologists interested in adding engineering and materials science approaches to both basic and translational science research.

How do you spend your free time?

As a tenure-tracker I don't have too much free time (self-inflicted), but I enjoy spending time outdoors, camping and backpacking, and love to travel and visiting breweries. I also enjoy tabletop RPGs and highly suggest Gloomhaven for anyone that likes D&D but wants something quicker to set up.



Kaitlyn Sadtler, Ph.D.

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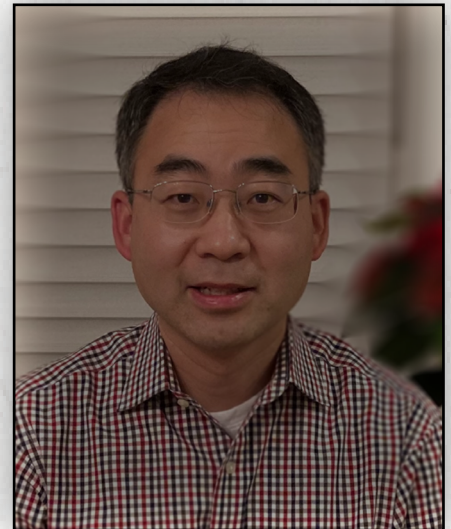
SPOTLIGHT

Dr. Wang is a principal investigator in the Laboratory of Vector-borne Viral Diseases, Division of Viral Products, Office of Vaccines Research and Review, FDA. To learn more about his work visit:

<https://www.fda.gov/vaccines-blood-biologics/biologics-research-projects/understanding-interplay-between-host-immunity-and-viral-factors-rational-design-vaccines-against>

Tell us about your science.

Historically the research effort of the laboratory of Vector-borne Viral Diseases (LVVD) makes use of the tools of molecular biology in order to elucidate mechanisms of flavivirus replication as they may relate to strategies for attenuation of flavivirus virulence and thereby enhance vaccine safety. Since 2020, we have been focusing on understanding safety and efficacy of COVID-19 vaccines. To this end, our laboratory has developed a genetic approach to attenuate SARS-CoV-2 as a nasal vaccine platform. Using an aged Syrian hamster model, we are evaluating the mucosal immunogenicity, transmission, and efficacy of this attenuated SARS-CoV-2 vaccine candidate.



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

As a child, I liked to crouch down and kneel on the dirt to watch how ants touch each other in the head, hoping I would be able to understand how they communicate. I took an immunology class during my second year in college. My teaching assistant, a nice graduate student who was afraid of handling mice, told us the appalling aspect that human immunodeficiency virus attacks our immune cells. At that moment, I felt that studying immunology could be a future career for me.

Tony Wang, Ph.D.

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

My Ph.D. adviser, Dr. Bruce Zwillig at The Ohio State University, was most influential to my career trajectory (although I did not follow his advice of doing a postdoctoral training at the NIH). He was completely hands-off and let me try things that interested me the most. I had opportunities to try different research topics, from innate immunity to mass spectrometry, and to virology. Let your interest guide you.

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

There are too many possible significant research/medical advances in the next 5-10 years, but I am mostly excited at the fact that AlphaFold is predicting protein structures from amino acid sequences. I hope AI systems could be developed to understand the human immunome.

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

The awesome speakers, the collaborations, and many young aspiring scientists.

How do you spend your free time?

Watching sports, playing guitar, cooking, and very recently I have decided to re-learn Calculus.

2022 IIG Workshop

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

The upcoming 2022 IIG Workshop will take place as a hybrid meeting, with both in-person and virtual attendance options. This will be the IIG's first in-person meeting since the onset of the pandemic!

The meeting will take place in the Natcher Conference Center (Building 45) on Thursday, December 8 and Friday, December 9.

In-person attendees will be expected to follow current NIH COVID-19 workplace guidance.

In addition to in-person poster sessions, posters will be uploaded to an on-line website currently under development. We expect on-line posters will be available prior to the meeting to help everyone prepare.

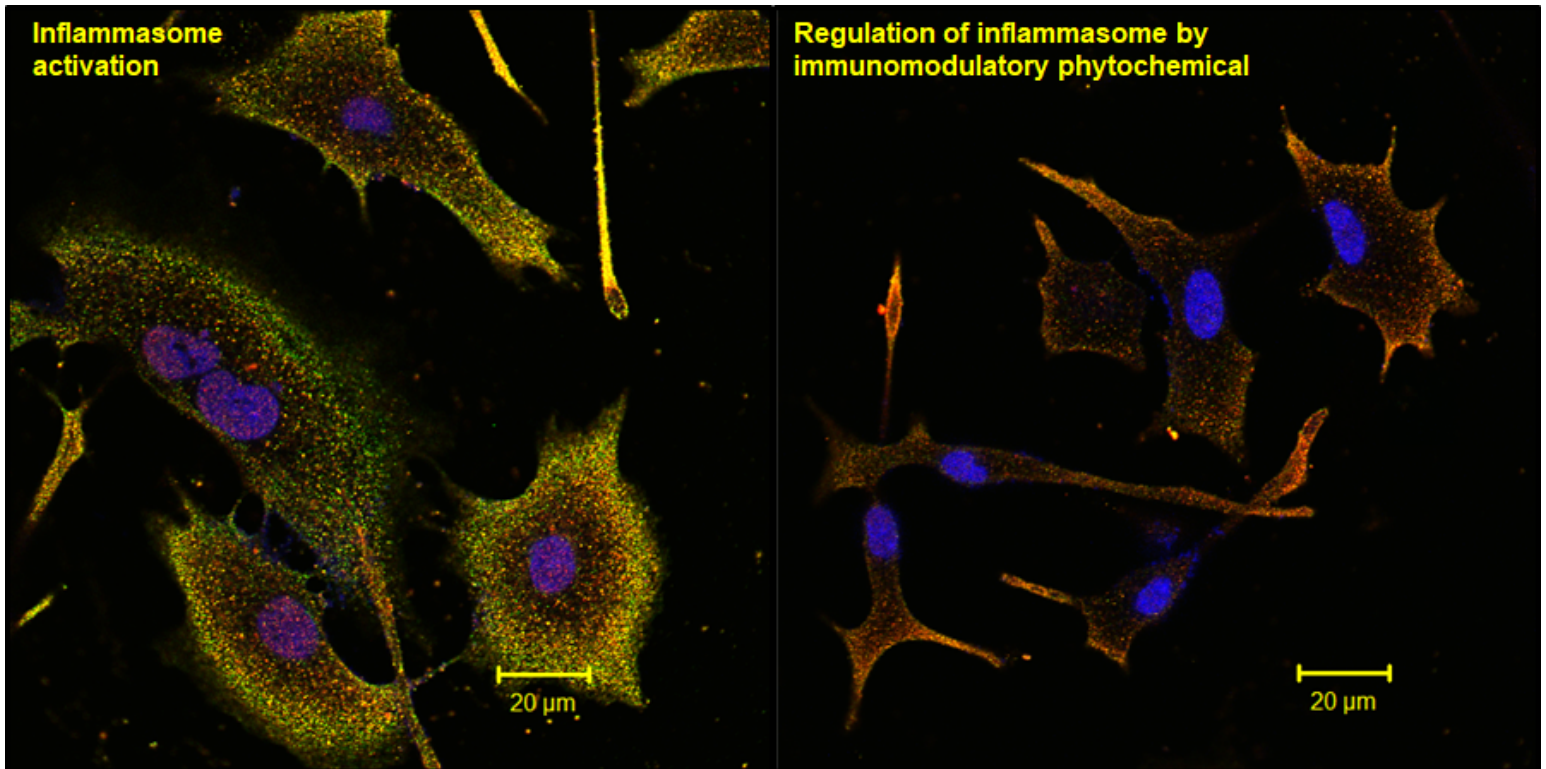
The program agenda and additional meeting related information can be found at:
<https://events.cancer.gov/eib/iig/agenda>

We looking forward to seeing everyone!



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

Phytochemical from dietary resource exerts innate immunity by regulating lung inflammasome



Lung cancer cell line A549 cells were activated for inflammasome in vitro overnight and in next set it was treated with immunomodulatory phytochemical derived from dietary plant product, prior to activation.

A549 lung cells exhibit increased expression and colocalization of AIM2 (red) and Caspase-1 (green) intermediates of inflammasome pathway which relate to overactivated inflammatory and pathogenic conditions. However, phytochemical treatment brings about substantial change in curbing ill-effects of inflammasome.

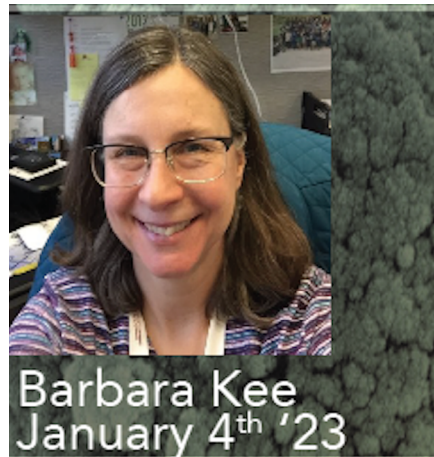
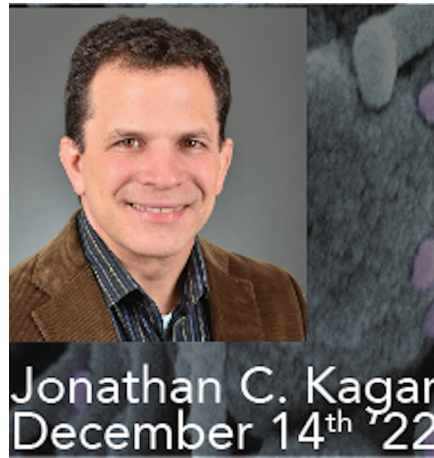
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Immunology Interest Group **SEMINAR SERIES**

Upcoming seminars



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<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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that join the lab:

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