

NIH-FDA IIG

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

NEWSLETTER

MARCH 2021

PUBLICATIONS

Systematic evaluation of nine monogenic autoinflammatory diseases reveals common and disease-specific correlations with allergy-associated features.

Schwartz DM, Kitakule MM, Dizon BL, Gutierrez-Huerta C, Blackstone SA, Burma AM, Son A, Deutch N, Rosenzweig S, Komarow H, Stone DL, Jones A, Nehrebecky M, Hoffmann P, Romeo T, de Jesus AA, Alehashemi S, Garg M, Torreggiani S, Montealegre Sanchez GA, Honer K, Souto Adeva G, Barron KS, Aksentijevich I, Ombrello AK, Goldbach-Mansky R, Kastner DL, Milner JD, Frischmeyer-Guerrero P. *Ann Rheum Dis.* 2021 Feb 22;annrheumdis-2020-219137. doi: 10.1136/annrheumdis-2020-219137. Online ahead of print. PMID: 33619160

We investigated the prevalence of allergy-associated clinical and immunological phenotypes in nine monogenic autoinflammatory diseases. We found that Familial Mediterranean Fever (FMF) was associated with reduced Type 2 immune responses; Cryopyrin-Associated Periodic fever Syndrome (CAPS) was associated with an enhanced Type 2 immune signature; and Deficiency of ADA2 (DADA2) was associated with high rates of physician-diagnosed allergy but reduced Type 2 immune signature – suggesting that autoinflammation can manifest clinical phenotypes that masquerade as allergic disorders.

Time-resolved systems immunology reveals a late juncture linked to fatal COVID-19.

Liu C *, Martins AJ *, Lau WW *, Rachmaninoff N *, Chen J, Imberti L, Mostaghimi D, Fink DL, Burbelo PD, Dobbs K, Delmonte OM, Bansal N, Failla L, Sottini A, Quiros-Roldan E, Han KL, Sellers BA, Cheung F, Sparks R, Chun

TW, Moir S, Lionakis MS; NIAID COVID Consortium; COVID Clinicians, Rossi C, Su HC, Kuhns DB, Cohen JI, Notarangelo LD, Tsang JS. *Cell.* 2021 Feb 10;S0092-8674(21)00168-g. doi: 10.1016/j.cell.2021.02.018. Online ahead of print. PMID: 33713619 Free PMC article. <https://doi.org/10.1016/j.cell.2021.02.018>, * co-first authors

A quantitative disease severity metric was developed by integrating clinical data and circulating cytokines to capture finer shades of COVID-19 severity. Multimodal single-cell profiling and integrative analyses of COVID-19 patients over time reveal a late wave of diverging inflammatory and host immune responses that predicts recovery versus fatality.

MicroRNA-221 and -222 modulate intestinal inflammatory Th17 cell response as negative feedback regulators downstream of interleukin-23.

Mikami Y, Philips RL, Sciumè G, Petermann F, Meylan F, Nagashima H, Yao C, Davis FP, Brooks SR, Sun HW, Takahashi H, Poholek AC, Shih HY, Afzali B, Muljo SA, Hafner M, Kanno Y, O'Shea JJ. *Immunity.* 2021 Mar 9;54(3):514-525.e6. doi: 10.1016/j.immuni.2021.02.015. Epub 2021 Mar 2. PMID: 33657395

MiR-221/222 are induced by IL-23 and suppressed by TGF, and target Maf and IL23r for degradation, thereby serving as a negative feedback regulator to constrain otherwise feed-forward inflammatory Th17 cell responses downstream of IL-23 in the gut.

The helminth glycoprotein omega-1 improves metabolic homeostasis in obese mice through type 2 immunity-independent inhibition of food intake.

van der Zande HJP, Gonzalez MA, de Ruiter K, Wilbers

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RHP, García-Tardón N, van Huizen M, van Noort K, Pelgrom LR, Lambooj JM, Zawistowska-Deniziak A, Otto F, Ozir-Fazalalikhani A, van Willigen D, Welling M, Poles J, van Leeuwen F, Hokke CH, Schots A, Yazdanbakhsh M, Loke P, Guigas B. *FASEB J.* 2021 Feb;35(2):e21331. doi: 10.1096/fj.202001973R. PMID: 33476078 Free PMC article.

In this study, we characterize how a helminth derived molecule can alter the metabolic phenotype of obese mice. While some effects are dependent on type 2 immune responses, other effects are not.

Single-Cell Transcriptional Survey of Ileal-Anal Pouch Immune Cells From Ulcerative Colitis Patients.

Devlin JC, Axelrad J, Hine AM, Chang S, Sarkar S, Lin JD, Ruggles KV, Hudesman D, Cadwell K, Loke P. *Gastroenterology.* 2021 Feb 4:S0016-5085(20)35571-2. doi: 10.1053/j.gastro.2020.12.030. Online ahead of print. PMID: 33359089

In this study we utilize scRNA-seq analysis of pinch biopsy specimens to characterize the immune cell compartment in ulcerative colitis patients and performed a meta-analysis on previous datasets to confirm and associate single cell profiles with responses to treatment.

Trastuzumab Blocks the Receiver Function of HER2 Leading to the Population Shifts of HER2-Containing Homodimers and Heterodimers.

Zhao J, Mohan N, Nussinov R, Ma B, Wu WJ. *Antibodies (Basel).* 2021 Feb 4;10(1):7. doi: 10.3390/antib10010007. PMID: 33557368 Free PMC article.

We utilized molecular dynamics (MD) simulations to model the allosteric consequences of trastuzumab binding to HER2 homodimers and heterodimers and revealed that binding of trastuzumab to HER2 promoted an allosteric effect on HER2, in both tyrosine kinase domain and ectodomain of HER2. The molecular details of the simulation provide an atomic level description and molecular insight into the action of HER2-targeted antibody therapeutics.

A Novel Bispecific Antibody Targeting EGFR and VEGFR2 Is Effective against Triple Negative Breast Cancer via Multiple Mechanisms of Action.

Mohan, N.; Luo, X.; Shen, Y.; Olson, Z.; Agrawal, A.; Endo,

Y.; Rotstein, D.S.; Pelosof, L.C.; Wu, W.J. A Novel Bispecific Antibody Targeting EGFR and VEGFR2 Is Effective against Triple Negative Breast Cancer via Multiple Mechanisms of Action. *Cancers* 2021, 13, 1027. <https://doi.org/10.3390/cancers13051027>.

We developed a novel bispecific antibody (BsAb) targeting EGFR and VEGFR2 and investigated its anti-tumor activity using triple negative breast cancer cell (TNBC) and xenograft mouse models. Data indicate that anti-EGFR/VEGFR2 BsAb elicited more comprehensive anti-tumor activity via multiple mechanisms of action, including direct inhibition of EGFR and VEGFR2 in TNBC cells, and disruption of autocrine and paracrine pathways in TNBC and endothelial cells, compared to the individual parental mAbs.

Lessons learned: new insights on the role of cytokines in COVID-19.

Buszko, M., Nita-Lazar, A., Park, JH. et al. *March, Nat Immunol* (2021). <https://doi.org/10.1038/s41590-021-00901-9>

This is a meeting report summarizing the second NIH/FDA virtual COVID-19 and Cytokines symposium that was held on 1 December 2020. It focused on longitudinal studies of COVID-19 immunity, including long-term consequences, potential associations with autoimmunity and the multisystem inflammatory syndrome in children (MIS-C).

Interrogation of the cellular immunome of cancer patients with regard to the COVID-19 pandemic.

Donahue RN, Marté JL, Goswami M, Toney NJ, Tsai YT, Gulley JL, Schlom JJ. *Immunother Cancer.* 2021 Mar;9(3):e002087. doi: 10.1136/jitc-2020-002087. PMID: 33707314 Review.

In addition to the development of preventive vaccines primarily designed to induce antibodies to the SARS-CoV-2 spike protein, emphasis should be placed on vaccines designed to also enhance cellular immune responses; these cellular immune responses should both be directed to the spike protein and to internal components of the SARS-CoV-2 virion. The cell-based and soluble factor assays described may also be employed in the analysis of the effects of various antivirals and other potential anti-SARS-CoV-2 therapeutics on the cellular immunome, and in the study of the pathogenesis of SARS-CoV-2 infections.

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Vaccine Increases the Diversity and Activation of Intratumoral T Cells in the Context of Combination Immunotherapy.

Horn LA, Fousek K, Hamilton DH, Hodge JW, Zebala JA, Maeda DY, Schlom J, Palena C. *Cancers (Basel)*. 2021 Feb 25;13(5):968. doi: 10.3390/cancers13050968.PMID: 33669155 Free article.

This study highlights the mechanistic synergy between vaccine and combination checkpoint immunotherapy and provides rationale for an ongoing clinical trial combining a cancer vaccine with bintrafusp alfa plus SX-682 therapy in patients with advanced solid tumors (NCT04574583).

Differential combination immunotherapy requirements for inflamed (warm) tumors versus T cell excluded (cool) tumors: engage, expand, enable, and evolve.

Fabian KP, Padgett MR, Fujii R, Schlom J, Hodge JW. *J Immunother Cancer*. 2021 Feb;9(2):e001691. doi: 10.1136/jitc-2020-001691.PMID: 33602696 Free PMC article.

A hexatherapy regimen composed of adenovirus-based vaccine and IL-15 (interleukin-15) superagonist (N-803) to engage the immune response; anti-OX40 and anti-4-1BB to expand effector cells; anti-PD-L1 to enable anti-tumor activity; and docetaxel to promote antigen spread was designed and administered to MC38-CEA (warm) and 4T1 (cool) murine tumor models. This strategic combination of immuno-oncology agents that can engage, expand, enable, and evolve the immune response can provide therapeutic benefits in both warm and cool tumor models.

Next Generation Therapeutic Strategies: Evolving cancer immunotherapy through agents that Engage, Expand and Enable the anti-tumor immune response [review].

Wolfson B and Hodge JW. *ImmunoMedicine*. Jan. 21, 2021. <https://onlinelibrary.wiley.com/doi/epdf/10.1002/imed.1020>.

In this review we summarize prior and ongoing Phase II and III clinical trials built upon the foundation of viral therapeutic cancer vaccines, examining their efficacy as a monotherapy, and more importantly, when combined with additional agents that Expand and Enable the immune system. The future of cancer immunotherapy will include evolving treatment strategies made

up of multiple agents, and we are optimistic that in this context viral therapeutic cancer vaccines will emerge as an important part of next generation effective therapeutic strategies.

Microbiota as Drivers and as Therapeutic Targets in Ocular and Tissue Specific Autoimmunity.

Salvador R, Zhang A, Horai R, Caspi RR. *Front Cell Dev Biol*. 2021 Feb 5;8:606751. doi: 10.3389/fcell.2020.606751. eCollection 2020.PMID: 33614621 Free PMC article. Review.

This review summarizes recent findings on the contribution of intestinal microbiota to T cell-driven, tissue-specific autoimmunity, with an emphasis on autoimmune uveitis, and analyzes the impact of microbiota-altering interventions. We discuss more translational animal models as well as integrating "multi-omics" data, to gain a better understanding of how gut microbiota can directly or indirectly modulate the immune system and contribute to autoimmune in distal tissues.

Regulated Tristetraprolin Overexpression Dampens the Development and Pathogenesis of Experimental Autoimmune Uveitis.

Xu B, Tang J, Lyu C, Wandu WS, Stumpo DJ, Mattapallil MJ, Horai R, Gery I, Blackshear PJ, Caspi RR. *Front Immunol*. 2021 Jan 25;11:583510. doi: 10.3389/fimmu.2020.583510. eCollection 2020.PMID: 33569048.

Tristetraprolin (TTP) negatively regulates of cytokines by affecting mRNA stability. We demonstrate that a gain-of-function mutation in TTP dampens autoimmune uveitis in the mouse model. TTP mutant mice had enhanced Treg frequency and a defect in autoimmune T cell priming due to deficient dendritic cell function. Augmentation of TTP should be explored as a therapeutic approach to uveitis.

Immunologic Control of HIV-1: What Have We Learned and Can We Induce It?

Rogan DC, Connors M. *Curr HIV/AIDS Rep*. 2021 Mar 11. doi: 10.1007/s11904-021-00545-2. Epub ahead of print. PMID: 33709324.

A large amount of data now exists on the virus-specific immune response associated with spontaneous or induced immunologic control of lentiviruses. This review focuses on how the current understanding of HIV-specific immunity might be leveraged into induction of immunologic control and what further research is needed to accomplish this goal.

Fasting-induced FOXO4 blunts human CD4⁺ T helper cell responsiveness.

Han K, Singh K, Rodman MJ, Hassanzadeh S, Wu K, Nguyen A, Huffstutler RD, Seifuddin F, Dagur PK, Saxena A, McCoy JP, Chen J, Biancotto A, Stagliano KER, Teague HL, Mehta NN, Pirooznia M, Sack MN. *Nat Metab.* 2021 Mar;3(3):318-326. doi: 10.1038/s42255-021-00356-0. Epub 2021 Mar 15. PMID: 33723462.

In a human study volunteers were subjected to fasting and refeeding protocols. RNAseq and flow cytometry identified robust effects on CD4 T cells. Subsequent bioinformatic and genetic manipulation studies identified the FOXO4-FKBP5 as a fasting induced regulatory program to blunt Th1 and Th17 responsiveness.

PD-1 immunobiology in glomerulonephritis and renal cell carcinoma.

FCurran CS, Kopp JB. *BMC Nephrol.* 2021 Mar 6;22(1):80. doi: 10.1186/s12882-021-02257-6. PMID: 33676416.

The expression and function of PD-1 family molecules on immune and kidney parenchymal cells were reviewed in the healthy kidney, glomerulopathies, renal cell carcinoma, and PD-1 immunotherapy-induced nephrotoxicity. Dysregulated vitamin D₃, glutathione, and/or AMP-activated protein kinase cell signals in chronic kidney disease may alter the PD-1-axis and promote the development of glomerulopathies as an adverse event associated with PD-1 immunotherapies.

Mechanisms contributing to ado-trastuzumab emtansine (T-DM1)-induced toxicities: a gateway to better understanding ADC-associated toxicities.

Yukinori Endo, Nishant Mohan, Milos Dokmanovic, Wen Jin Wu. *Antibody Therapeutics*, 2021; tbab005, <https://doi.org/10.1093/abt/tbab005>

In this review article, we summarized the results from our laboratory showing that ado-trastuzumab emtansine (also known as T-DM1) binds to cytoskeleton-associated protein 5 (CKAP5) on the cell surface of hepatocytes via its payload component (DM1) and that this interaction is independent of HER2, leading to cell growth inhibition and apoptosis of hepatocytes in a T-DM1 dose dependent manner. This review highlights the importance of HER2-independent mechanism of T-DM1 to induce hepatotoxicity, which offers a new insight into a role for CKAP5 in the overall maytansinoid (DM1 and DM4)-based antibody-drug conjugate (ADC)-mediated cytotoxicity and opens a new avenue for developing the next generation of ADCs.

A human monoclonal antibody blocks malaria transmission and defines a highly conserved neutralizing epitope on gametes.

Coelho CH et al. *Nature Communications.* 2021 March 19 <https://doi.org/10.1038/s41467-021-21955-1>.

We described LMIV230-01, a human mAb that binds to gametes – the stage that initiates mosquito infection. LMIV230-01 binds to other P. falciparum strains and the epitope is large and very conserved. It is present in varying concentrations in serum of vaccinees.

TCR-engineered T cells targeting E7 for patients with metastatic HPV-associated epithelial cancers.

Nagarsheth NB, Norberg SM, Sinkoe AL, Adhikary S, Meyer TJ, Lack JB, Warner AC, Schweitzer C, Doran SL, Korrapati S, Stevanović S, Trimble CL, Kanakry JA, Bagheri MH, Ferraro E, Astrow SH, Bot A, Faquin WC, Stroncek D, Gkitsas N, Highfill S, Hinrichs CS. *Nat Med.* 2021 Mar;27(3):419-425. doi: 10.1038/s41591-020-01225-1. Epub 2021 Feb 8. PMID: 33558725.

First-in-human phase I trial using T cells genetically engineered to express a T cell receptor targeting HPV-16 specific E7 for treatment of metastatic HPV+ cancers. Robust tumor regression was observed, including in patients resistant to checkpoint blockade. Translational research highlights major tumor intrinsic genomic mutations and copy losses leading to evasion of T cell therapy.

Improving the Odds in Advanced Breast Cancer With Combination Immunotherapy: Stepwise Addition of Vaccine, Immune Checkpoint Inhibitor, Chemotherapy, and HDAC Inhibitor in Advanced Stage Breast Cancer

Gatti-Mays ME, Gameiro SR, Ozawa Y, Knudson KM, Hicks KC, Palena C, Cordes LM, Steinberg SM, Francis D, Karzai F, Lipkowitz S, Donahue RN, Jochems C, Gulley JL, Schlom J. *Frontiers in Oncology (Women's Cancer section)*, March 5, 2021.

We hypothesize that the combination of BN-Brachyury vaccine, bintrafusp alfa, entinostat and ado-trastuzumab emtansine will induce a robust immune response against HER2+ breast cancer with improved response rates when compared to historical controls. Enhancing immunity via several complementary mechanisms is a promising means to produce objective responses in an ever-increasing portion of patients who may benefit from immunotherapy.

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Characterization of a recombinant gorilla-adenovirus HPV therapeutic vaccine (PRGN-2009).

Pellom ST, Smalley Rumfield C, Morillon YM II, Roller N, Poppe LK, Brough DE, Sabzevari H, Schlom J, Jochems C. JCI Insight. 2021 Mar 2;141912. doi: 10.1172/jci.insight.141912. Online ahead of print. PMID: 33651712 Free article.

These studies provide the first evaluation of a therapeutic recombinant gorilla adenovirus HPV vaccine, PRGN-2009, showing promising preclinical anti-tumor efficacy and induction of HPV-specific T cells for use in HPV positive malignancies. These studies provide the rationale for its evaluation in clinical trials. A phase I study of PRGN-2009 alone, or in combination with bintrafusp alfa, is currently ongoing at the National Cancer Institute, NIH (NCT04432597).

Immunology of Lynch Syndrome [review].

Pastor DM and Schlom J
Current Oncology Reports, MS accepted 2/18/21.

Patients with Lynch syndrome have a high probability of developing colorectal and other carcinomas. This review provides a comprehensive assessment of the immunologic aspects of Lynch syndrome pathogenesis, and provides an overview of potential immune interventions for patients with Lynch syndrome polyps and Lynch syndrome-associated carcinomas.

CONGRATULATIONS!

Dr. Toshi Nakayama

Immense kudos and congratulations to Dr. Toshi Nakayama, a former NCI postdoctoral fellow, and IIG alum, who has become the President of Chiba University starting April 1, 2021. Dr. Nakayama did his postdoc work with Al Singer in NCI and returned to Chiba University to rise through academics, making numerous advances in understanding the biology of Th2 cells. Chiba University has about 14,000 undergraduate and graduate students and 3,000 professors and administrative staff. Dr. John O'Shea and the NIH-FDA IIG community wish Dr. Nakayama the best in his new prestigious and challenging position.



Dr. Toshi Nakayama

CONGRATULATIONS



Dr. Michael J. Lenardo

Michael J. Lenardo, NIAID, NIH has received the 2020 AAI-Steinman Award for Human Immunology Research.

This award is for his significant, sustained achievement in immunology research contributing to the understanding of immune processes underlying human disease pathogenesis, prevention, and therapies.

<https://www.aai.org/Awards/Career/AAI-Steinman-Award-for-Human-Immunology-Research>



Dr. Susan K. Pierce

Susan K. Pierce, NIAID, NIH has received the 2020 AAI-BioLegend Herzenberg Award.

This award is for her exemplary research contributions to the field of B cell biology.

aai.org/Awards/Career/AAI-Herzenberg-Award

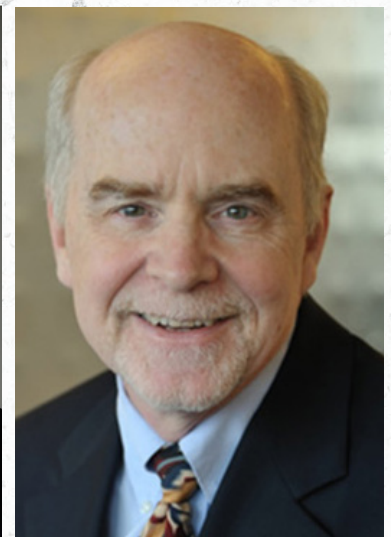
Drs. Warren Leonard and John O'Shea have received the International Harrington Prize

The eighth annual Harrington Prize for Innovation in Medicine has been jointly awarded to Warren J. Leonard, MD, NHLBI, NIH Distinguished Investigator, and John J. O'Shea, MD, Scientific Director, NIAMS, NIH, for their respective contributions to the field of immunology, from fundamental discovery to therapeutic impact. In addition to receiving a \$20,000 honorarium, co-recipients Dr. Leonard and Dr. O'Shea will deliver The Harrington Prize Lecture at the 2021 AAP/ASCI/APSA Joint Meeting, will be featured speakers at the 2021 Harrington Scientific Symposium, and will co-publish an essay in the Journal of Clinical Investigation.

<https://www.prnewswire.com/news-releases/international-harrington-prize-jointly-awarded-to-drs-warren-leonard-and-john-oshea-301255000.html>



Dr. Warren Leonard



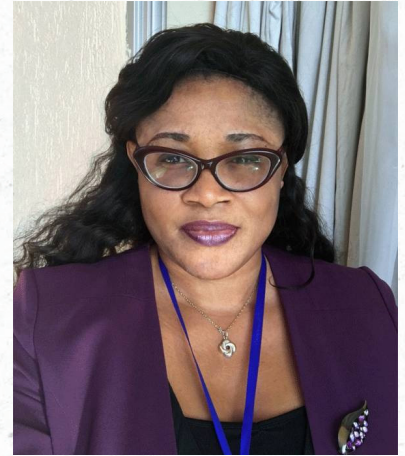
Dr. John O'Shea

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CELEBRATING WOMEN IN SCIENCE

Dr. Enitome Bafor, Postdoctoral Fellow in Dr. Howard Young's lab was recently recognized and awarded the Hello Bio Lab Hero Award.

<https://www.hellobio.com/blog/meet-our-lab-heroes-awards-2018-winner-dr-enitome-bafor.html>



Dr. Enitome Bafor

INFLAMMATORY BRAIN DISORDERS CONFERENCE

**Foundation For Children With Neuroimmune Disorders Inflammatory Brain
Disorders Conference (Virtual)**

https://emedeventslive.s3-us-west-2.amazonaws.com/uploads/newsletters/2021-02-22/FCND_v1.html