NIH-FDA IIG

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

NEWSLETTER

SEPTEMBER 2021

PUBLICATIONS

Overcoming Acquired Epigenetic Resistance to BTK Inhibitors.

Arthur L. Shaffer III, James D. Phelan, James Q. Wang, DaWei Huang, George W. Wright, Monica Kasbekar, Jaewoo Choi, Ryan M. Young, Daniel E. Webster, Yandan Yang, Hong Zhao, Xin Yu, Weihong Xu, Sandrine Roulland, Michele Ceribelli, Xiaohu Zhang, Kelli M. Wilson, Lu Chen, Crystal McKnight, Carleen Klumpp-Thomas, Craig J. Thomas, Björn Häupl, Thomas Oellerich, Zachary Rae, Michael C. Kelly, Inhye E. Ahn, Clare Sun, Erika M. Gaglione, Wyndham H. Wilson, Adrian Wiestner and Louis M. Staudt
Blood Cancer Discov October 7 2021 DOI:10.1158/2643-3230.BCD-21-0063

In diffuse large B cell lymphoma, which depends upon oncogenic BCR signaling, we show that primary resistance to BTK inhibitors is due to epigenetic changes that circumvent the BTK blockade by replacing its PLCG2-activating function with RAC2. We also observed this resistance mechanism in chronic lymphocytic leukemia, suggesting that epigenetic alterations may contribute more to BTK inhibitor resistance than currently appreciated.

Pulmonary infection induces persistent, pathogen-specific lipidomic changes influencing trained immunity.

Roberts LM, Schwarz B, Speranza E, Leighton I, Wehrly T, Best S, Bosio CM. iScience. 2021 Aug 24;24(9):103025. doi: 10.1016/j.isci.2021.103025. eCollection 2021 Sep 24.PMID: 34522865.

Using multi-omics, we found pathogens differentially affect pulmonary efferocytosis within macrophages after the host resolves the infection and result in unique lipid mediator profiles in the lung. These changes in the lipid landscape correlate with impacts on the trained immunity response to an unrelated infection.

Functional inactivation of pulmonary MAIT cells following 5-OP-RU treatment of non-human primates.

Sakai S, Lora NE, Kauffman KD, Dorosky DE, Oh S, Namasivayam S, Gomez F, Fleegle JD; Tuberculosis Imaging Program, Arlehamn CSL, Sette A, Sher A, Freeman GJ, Via LE, Barry Iii CE, Barber DL.Mucosal Immunol. 2021 Sep;14(5):1055-1066. doi: 10.1038/s41385-021-00425-3. Epub 2021 Jun 22.PMID: 34158594.

Although the mouse model is a powerful tool that has revealed much about MAIT cell biology, there may be important instances where MAIT cell responses in mice may not be representative of responses in macaques and by extension also not representative of in vivo MAIT cell responses in humans. The development of strategies to induce large populations of highly functional MAIT cells in macaques is needed to evaluate their clinical potential as targets of vaccines and therapeutics in humans.

Anti-Carbamylated LL37 Antibodies Promote Pathogenic Bone Resorption in Rheumatoid Arthritis.

O'Neil LJ, Oliveira CB, Sandoval-Heglund D, Barrera-Vargas A, Merayo-Chalico J, Aguirre-Aguilar E, Kaplan MJ, Carmona-Rivera C.Front Immunol. 2021 Sep 14;12:715997. doi: 10.3389/fimmu.2021.715997. eCollection 2021.PMID: 34594331

We found that antibodies against carbamylated form of that antimicrobial peptide LL37 were present in Rheumatoid Arthritis patients (RA). Anti-carLL37 Abs promote formation of osteoclast and bone resorption. Our findings shed light on mechanisms associated with the presence of anti- carbamylated proteins Ab (anti-carP) in RA patients and their association with worse prognosis..

Continued>>

Human oral mucosa cell atlas reveals a stromal-neutrophil axis regulating tissue immunity.

Williams DW, Greenwell-Wild T, Brenchley L, Dutzan N, Overmiller A, Sawaya AP, Webb S, Martin D; NIDCD/NIDCR Genomics and Computational Biology Core, Hajishengallis G, Divaris K, Morasso M, Haniffa M, Moutsopoulos NM.Cell. 2021 Jul 22;184(15):4090-4104.e15. doi: 10.1016/j.cell.2021.05.013. Epub 2021 Jun 14.PMID: 34129837.

We compile a single-cell transcriptome atlas of human oral mucosa in healthy individuals and patients with periodontitis. Our work provides a resource characterizing the role of tissue stroma in regulating mucosal tissue homeostasis and disease pathogenesis.

Circulating CD138 enhances disease progression by augmenting autoreactive antibody production in a mouse model of systemic lupus erythematosus.

Liu L, Akkoyunlu M.J Biol Chem. 2021 Sep;297(3):101053. doi: 10.1016/j.jbc.2021.101053. Epub 2021 Aug 6.PMID: 34364875

In this study, we show that trypsin mediated cleavage of CD138 from MRL/Lpr mice CD4+ T cells contributes to the increase in circulating CD138 (syndecan-1) levels as the disease progresses. Soluble CD138 promotes anti-dsDNA antibody production by binding to APRIL and enhancing APRIL mediated plasma cell generation from autoreactive B cells in lupus mouse.

Intracellular Accumulation of IFN-4 Induces ER Stress and Results in Anti-Cirrhotic but Pro-HCV Effects.

Onabajo OO, Wang F, Lee MH, Florez-Vargas O, Obajemu A, Tanikawa C, Vargas JM, Liao SF, Song C, Huang YH, Shen CY, Banday AR, O'Brien TR, Hu Z, Matsuda K, Prokunina-Olsson L. Front Immunol. 2021 Aug 23;12:692263. doi: 10.3389/fimmu.2021.692263. eCollection 2021.PMID: 34497603

Our results suggest that the molecular mechanisms underlying the anti-cirrhotic but pro-HCV associations observed for IFNL3/IFNL4 polymorphisms are, at least in part, contributed by intracellular accumulation of IFN-4 causing ER stress in hepatic cells.

Using PET imaging to track STING-induced interferon signaling.

Bafor EE, Young HA.Proc Natl Acad Sci U S A. 2021 Sep 21;118(38):e2114839118. doi: 10.1073/pnas.2114839118. PMID: 34521758.

This article is a commentary on the work by Liang et al., 2021 (1), where the authors utilized [18F] FLT PET imaging to monitor STING agonist-induced IFN signaling in pancreatic ductal adenocarcinoma (PDAC) model. The commentary highlights the article's strengths, the potential usefulness of the technique and provides additional suggestions to improve the article.

Concordance of immunological events between intrarectal and intravenous SHIVAD8-EO infection when assessed by Fiebig-equivalent staging.

Dias J, Fabozzi G, March K, Asokan M, Almasri CG, Fintzi J, Promsote W, Nishimura Y, Todd JP, Lifson JD, Martin MA, Gama L, Petrovas C, Pegu A, Mascola JR, Koup RA.J Clin Invest. 2021 Sep 1;131(17):e151632. doi: 10.1172/JCI151632.PMID: 34623326.

In this study, we identified and extensively characterized the Fiebig-equivalent stages of SHIVAD8-EO infection in rhesus macaques challenged intrarectally or intravenously with SHIVAD8-EO. We showed concordance of immunological events between intrarectal and intravenous SHIVAD8-EO infection when evaluated by Fiebig-equivalent staging, despite differences in infection progression between the challenge groups.

IL-7 in SARS-CoV-2 Infection and as a Potential Vaccine Adjuvant.

Bekele Y, Sui Y, Berzofsky JA.Front Immunol. 2021 Sep 17;12:737406. doi: 10.3389/fimmu.2021.737406. eCollection 2021.PMID: 34603318.

This is a review of the role of IL-7 as a marker of disease severity, as a possible treatment, and as a potential vaccine adjuvant.

Continued>>

Disruption of the endopeptidase ADAM10-Notch signaling axis leads to skin dysbiosis and innate lymphoid cell-mediated hair follicle destruction.

Sakamoto K, Jin SP, Goel S, Jo JH, Voisin B, Kim D, Nadella V, Liang H, Kobayashi T, Huang X, Deming C, Horiuchi K, Segre JA, Kong HH, Nagao K.Immunity. 2021 Sep 22:S1074-7613(21)00364-2. doi: 10.1016/j.immuni.2021.09.001. Online ahead of print.PMID: 34582748.

Host symbiosis with commensal microorganisms must be maintained during homeostasis and inflammation. We show that the innate epithelial barrier bolstered by ADAM10-Notch signaling in type I interferon-responsive upper hair follicles was crucial for regulating the follicular microbiome, inhibition of which led to downregulation of b-defensin-6, dysbiosis, and inflammatory destruction of hair follicles mediated by innate lymphoid cells.

Tumour-targeted interleukin-12 and entinostat combination therapy improves cancer survival by reprogramming the tumour immune cell landscape.

Hicks KC, Chariou PL, Ozawa Y, Minnar CM, Knudson KM, Meyer TJ, Bian J, Cam M, Schlom J, Gameiro SR.Nat Commun. 2021 Aug 26;12(1):5151. doi: 10.1038/s41467-021-25393-x.PMID: 34446712

Our preclinical research has demonstrated that combining Entinostat with NHS-IL12 elicits significant and sustained antitumor efficacy and tumor eradication by shifting the tumor immunome to a functionally inflamed landscape through the concerted action of CD8+ tumor-infiltrating lymphocytes, M1 macrophages and neutrophils. These findings provide a rationale for utilizing this combination immunotherapy in the clinical setting..

Continued>>

CONGRATULATIONS TO OUR VERY OWN DR. KAREN ELKINS

for her selection as the permanent Associate Director of Science (ADS) at FDA!

The ADS is a key member of Center for Biologics Evaluation and Research (CBER) Senior Leadership Team and is responsible for high-level strategy, promotion, and coordination of all scientific research activities conducted by the Center and assuring their high quality, focus, and scientific and public health outcomes.

Dr. Elkins spent the last few months on a detail to the CBER Immediate Office of the Director (IOD), supporting the Center's efforts in developing and implementing a research agenda. In her role as ADS, she will continue those efforts and lead the development of an overall strategy to address emerging scientific issues that affect CBER-regulated products.

Dr. Elkins has a long history with the FDA-CBER research program. She joined CBER/Office of Vaccines Research and Review (OVRR) in 1993 as a principal investigator and regulatory reviewer. Her lab studies protective immunity to intracellular bacteria, including Mycobacterium tuberculosis and Francisella tularensis, and seeks to identify correlates of vaccine-induced protection. Dr. Elkins has contributed to various scientific initiatives within the FDA and has served as a mentor for research and professional development training and is actively involved in mediating FDA-NIH partnerships. Externally, Karen represents CBER on CDC and NIH committees and is active in several professional societies. Dr. Elkins also contributes to grant reviews, peer-reviews for several journals and teaches microbiology and science writing.

Dr. Elkins received her undergraduate degree in Chemistry from Wake Forest, her Ph.D. in Microbiology and Immunology at Duke, and an M.A. in Science Writing from Johns Hopkins University. Following her postdoctoral training at USUHS and NIH, she established her laboratory at the Walter Reed Army Institute of Research before joining CBER in 1993.

The NIH-FDA committee and the IIG community would like to congratulate Dr. Elkins on her new role as the Associate Director of Science at CBER, FDA.

Dr. Karen Elkins