NIH-FDA IIG NEWSLETTER

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

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PUBLICATIONS

SARS-CoV-2 drives JAK1/2-dependent local complement hyperactivation.

Yan B†, Freiwald T†, Chauss D†, Wang L†, West E†, Mirabelli C†, Zhang CJ, Nichols EM, Malik N, Gregory R, Bantscheff M, Ghidelli-Disse S, Kolev M, Frum T, Spence JR, Sexton JZ, Alysandratos KD, Kotton DN, Pittaluga S, Bibby J, Niyonzima N, Olson MR, Kordasti S, Portilla D, Wobus CE, Laurence A, Lionakis MS, Kemper C*, Afzali B*, Kazemian M*.Sci Immunol. 2021 Apr 7;6(58):eabg0833. doi: 10.1126/sciimmunol.abg0833.PMID: 33827897
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Here we show that one of the most significant pathways induced by SARS-CoV2 infection of respiratory epithelial cells is the complement system. Genes of this pathway, including complement factor (C3) and factor B (CFB), are induced in a JAK1/2-STAT1-dependent manner downstream of interferon signaling. C3 protein is processed intracellularly to active C3a by CFB, reflecting the presence of a novel inducible cell-intrinsic alternative complement pathway convertase. Active C3 fragments ligated their cognate receptors on immune cells in the lungs to drive inflammation. Accordingly, cell-permeable inhibitors of CFB, or Ruxolitinib, a JAK1/2 inhibitor, either alone or in combination with Remdesivir, blocked C3a generation from infected cells.

SIGNAL: A web-based iterative analysis platform integrating pathway and network approaches optimizes hit selection from genome-scale assays.

Katz S, Song J, Webb KP, Lounsbury NW, Bryant CE, Fraser IDC.Cell Syst. 2021 Apr 21;12(4):338-352.e5. doi: 10.1016/j.cels.2021.03.001. Epub 2021 Mar 24.PMID: 33894945

We describe SIGNAL a hit selection analysis platform that prioritizes candidates from omics data by using two cutoffs and through iterative pathway enrichment and network analysis, optimally offsets the trade-offs of each. SIGNAL is publicly available as a web-based application (https://signal.niaid.nih.gov).

IFNs Reset the Differential Capacity of Human Monocyte Subsets to Produce IL-12 in Response to Microbial Stimulation.

Muglia Amancio A, Mittereder L, Carletti A, Tosh KW, Green D, Antonelli LR, Gazzinelli RT, Sher A, Jankovic D.J Immunol. 2021 Apr 1;206(7):1642-1652. doi: 10.4049/jimmunol.2001194. Epub 2021 Feb 24.PMID: 33627376

In this study, we showed that human peripheral blood CD16+ monocytes that are a major producer of IL-12 and TNF upon exposure to Toxoplasma gondii display an IFN-stimulated gene profile at baseline. Interestingly, priming by IFN-g or inhibition of the mTOR-pathway boosts the IL-12 secretion of the low responding CD16neg, but not CD16+, monocyte subset. In direct contrast to IFN-g, IFN-a priming fails to enhance monocyte IL-12 production and inhibits the response of both CD16+ and IFN-g-primed CD16neg populations.

High-throughput, single-copy sequencing reveals SARS-CoV-2 spike variants coincident with mounting humoral immunity during acute COVID-19.

Ko SH, Bayat Mokhtari E, Mudvari P, Stein S, Stringham CD, Wagner D, Ramelli S, Ramos-Benitez MJ, Strich JR, Davey RT Jr, Zhou T, Misasi J, Kwong PD, Chertow DS, Sullivan NJ, Boritz EA.PLoS Pathog. 2021 Apr 8;17(4):e1009431. doi: 10.1371/journal.ppat.1009431. eCollection 2021 Apr.PMID: 33831133 Free PMC article. Clinical Trial.

We used new technology to show that coronavirus variants with mutated spike proteins can arise early in the course of

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infection. Our results suggest more virus evolution in each person than previously thought, with potential implications for clinical outcomes and for the emergence of transmissible variant strains.

Virus-like particle-drug conjugates induce protective, long-lasting adaptive anti-tumor immunity in the absence of specifically targeted tumor antigens.

Kines RC, Thompson CD, Spring S, Li Z, de Los Pinos E, Monks S, Schiller JT.Cancer Immunol Res. 2021 Apr 14:canimm.0974.2019. doi: 10.1158/2326-6066.CIR-19-0974. Online ahead of print.PMID: 33853825 Free article.

AU-011 is composed of an HPV VLP conjugated to photoactivatable IRDye-700DX. Their broad, tumor-tropic nature combined with light-induced cytotoxic activity induces tumor immunogenic cell death, boosts anti-tumor immunity, and elicits long-term anti-tumor immunity.

Genetically engineered myeloid cells rebalance the core immune suppression program in metastasis.

Kaczanowska S, Beury DW, Gopalan V, Tycko AK, Qin H, Clements ME, Drake J, Nwanze C, Murgai M, Rae Z, Ju W, Alexander KA, Kline J, Contreras CF, Wessel KM, Patel S, Hannenhalli S, Kelly MC, Kaplan RN.Cell. 2021 Apr 15;184(8):2033-2052.e21. doi: 10.1016/j.cell.2021.02.048. Epub 2021 Mar 24.PMID: 33765443

The pre-metastatic niche is a myeloid-rich, T-cell-poor immunosuppressive microenvironment that promotes metastatic progression. To take advantage of the infiltration of myeloid cells into tumor and metastatic microenvironments, the authors genetically engineered myeloid cells, termed GEMys, to deliver IL-12 locally to metastatic sites to reverse the immune suppression program and to activate anti-tumor immunity.

Effect of an Adenovirus-Vectored Universal Influenza Virus Vaccine on Pulmonary Pathophysiology in a Mouse Model.

Dhakal S, Loube J, Misplon JA, Lo CY, Creisher PS, Mulka KR, Deshpande S, Mitzner W, Klein SL, Epstein SL.J Virol. 2021 Apr 12;95(9):e02359-20. doi: 10.1128/JVI.02359-20. Print 2021 Apr 12.PMID: 33627390.

Theoretical concerns have been raised in the literature that a vaccine administered directly to the respiratory tract and inducing potent local T-cell responses might lead to lung damage when infection was later encountered. We analyzed multiple parameters of lung function in the setting of such a vaccination andfound that despite CD8 T-cell responses in the lungs, lungs were not damaged and lung functions were normal after vaccination and during subsequent protection against infection.

Type I IFNs facilitate innate immune control of the opportunistic bacteria Burkholderia cenocepacia in the macrophage cytosol.

Dorrington MG, Bradfield CJ, Lack JB, Lin B, Liang JJ, Starr T, Ernst O, Gross JL, Sun J, Miller AH, Steele-Mortimer O, Fraser IDC.PLoS Pathog. 2021 Mar 8;17(3):e1009395. doi: 10.1371/journal.ppat.1009395. eCollection 2021 Mar.PMID: 33684179 Free PMC article.

We are regularly and periodically colonized by opportunistic pathogens like Burkholderia cenocepacia (Bc) yet, unless there are underlying conditions such ascystic fibrosis or primary immunodeficiency, most of us will clear these infections without any clinical symptoms of disease. We have found that one reason for this are the actions of type I interferons (IFNs). Intact type I IFN signaling protects mice from Bc, with wild-type mice lacking any clinical signs post-infection while mice lacking the type I IFN receptor (IFNAR) show significant (though non-fatal) illness. We show here through high-content imaging, RNA sequencing, and flow cytometry, that type I IFNs, but not IFN-, are vital to macrophage responses to Bc, supporting the ubiquitination of these bacteria in the cytosol and their subsequent destruction via autophagy. Therefore, type I IFNs are vital for our protection against potentially dangerous bacterial infections.

Analysis of the tumor microenvironment and anti-tumor efficacy of subcutaneous vs systemic delivery of the bifunctional agent bintrafusp alfa.

Yohei Ozawa, Kristin C. Hicks, Christine M. Minnar, Karin M. Knudson, Jeffrey Schlom & Sofia R. Gameiro. Oncoimmunology (2021) 10:1, DOI: 10.1080/2162402X.2021.1915561.

To our knowledge, this is the first preclinical evaluation of the delivery of bintrafusp alfa, a bifunctional agent that targets both PD-L1 and sequesters TGF, via systemic i.p. administration vs s.c. injection in the EMT6 breast tumor model and in the MC38 colorectal tumor model. These studies provide the rationale to explore whether the s.c. route of administration will attain similar efficacy in the clinic.

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CONGRATULATIONS

Congratulations to all the NIH fellows who received the 2021 AAI Trainee Abstract Award!

https://www.aai.org/Awards/Travel/AAI-Trainee-Abstract-Award/Current-Recipients

Joanna Marta Bandola-Simon	NCI
Tamara Haque	NIAID
Rodrigo A. Matus Nicodemos	NIAID
Abir Kumar Panda	NIAID
Sabina Kaczanowska	NCI
Mohammad Nizam Mansoori	NIAID
Nicolas S. Merle	NHLBI
Yayi Gao	NCI
Thomas Andreas Liechti	NIAID
Rachael Laura Philips	NIAMS
Orna Rabinovich-Ernst	NIAID
Camille A. Spinner	NCI

Congratulations to all the NIH fellows who received the 2021 AAI Late-Breaking Poster Award!

https://www.aai.org/Awards/Travel/AAI-Late-Breaking-Poster-Award/Current-Recipients

Shizuka Otsuka	NCI

CONGRATULATIONS!

Dr. Patrick Hwu

The NIH-FDA community would like to congratulate Dr. Patrick Hwu for being appointed as the president and CEO of Moffitt Cancer Center. Dr. Hwu is an alumnus of the NCI. He joined NCI as a summer student in Howard Young's lab to publish his first coauthorship manuscript. He earned his medical degree from The Medical College of Pennsylvania and completed a fellowship in oncology at the National Cancer Institute in the laboratory of Dr. Steven Rosenberg. During his appointment at MD Anderson, he was the Head of the Melanoma Immunotherapy program before starting his present position as the President and CEO of the Moffitt Cancer Center. The NIH-IIG community wish Dr. Hwu the best in his new prestigious position.

Dr. Patrick Hwu

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DR. MATTIA BONSIGNORI

A NEW TENURE-TRACK INVESTIGATOR IN THE DIR LABORATORY OF INFECTIOUS DISEASES

Dr. Bonsignori will be implementing an innovative program in antibody discovery, viral immunology, and translational immunobiology as Chief of the Translational Immunobiology Unit. Mattia's work will help develop novel vaccines and improve existing vaccine platforms. He also looks forward to collaborating to elucidate host immune responses against emerging and re-emerging viruses.

Mattia received his M.D. and M.S. in Clinical Microbiology and Virology from the University of Insubria Medical School, Varese, Italy. He conducted postdoctoral research at St. Jude Children's Research Hospital, Memphis, TN before being appointed as a Research Associate at the Duke Human Vaccine Institute. There he focused primarily on HIV vaccine development, becoming Associate Professor of Medicine and founder and director of the Laboratory of B-cell Repertoire Analysis. His high-throughput memory B cell culture system for functional screening of memory B cells provided a novel framework for steering the immune response through immunogen design based on the probability of individual mutations and their effect on antibody effector functions.

Mattia can be reached at mattia.bonsignori@nih.gov

Dr. Mattia Bonsignori

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NIH/FDA IIG WORKSHOP

SEPTEMBER 8 & 9 2021 ON THE COMPUTER NEAREST YOU

REGISTRATION IS OPEN!

https://events.cancer.gov/eib/iig

Registration is anticipated to remain open ***until Friday June 4, 2021***, space permitting.

In the past, the Workshop has been very popular and registration slots have filled very quickly. Although there is no physical space limitation, registration will still be closed the moment we reach virtual capacity. Acceptance will be on a strict first-come, first-served basis and favor those with science to share (i.e. with an abstract, details at the site). Please, register EARLY.

Things to Know:

- Registration does not equal acceptance. Official Acceptance will follow in a separate email from the IIG (likely a few weeks after you registered).
- Only those accepted will receive an electronic Abstract Book and an invitation to access the virtual workshop.
- Artwork submissions are encouraged and will be used in the program and Abstract Book for the Workshop!
- This year, poster presenters may have their own individual 'rooms' where they can present their work to colleagues who 'wander' by.
- The virtual workshop will not be recorded, so your active participation is highly encouraged.
- It is completely permissible to submit an abstract that you may have submitted or plan to submit to another meeting (e.g. AAI).
- Also, if you are new to the IIG and would like to submit an abstract covering immunology you did at your previous institution or hope to do for your NIH research project, such a submission is encouraged
- We will present 'travel' awards for stellar oral presentations and posters

Our Gurus this year:

Dr. Leslie Berg
Professor & Chairman,
Department of Immunology & Microbiology,
University of Colorado Anschutz School of Medicine

Dr. James Crowe
Ann Scott Carell Chair,
Departments of Pediatrics, Pathology, Microbiology and Immunology
Director, Vanderbilt Vaccine Center,
Vanderbilt University Medical Center