# NIH-FDA IIG

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

# NEWSLETTER

**MAY 2021**

## PUBLICATIONS

### One or two injections of MVA-vectored vaccine shields hACE2 transgenic mice from SARS-CoV-2 upper and lower respiratory tract infection.

Liu R, Americo JL, Cotter CA, Earl PL, Erez N, Peng C, Moss B.Proc Natl Acad Sci U S A. 2021 Mar 23;118(12):e2026785118. doi: 10.1073/pnas.2026785118. PMID: 33688035

*Modified vaccinia virus Ankara (MVA) is a replication-restricted smallpox vaccine, and numerous clinical studies of recombinant MVAs (rMVAs) as vectors for prevention of other infectious diseases, including COVID-19, are in progress. Here, we characterize the immunogenicity and ability to protect transgenic mice of rMVAs expressing the S protein of SARS-CoV-2 with modifications individually or in combination that include two proline substitutions to stabilize the prefusion form, mutations of the furin recognition site to prevent cleavage, and deletion of the endoplasmic retrieval signal to increase expression at the cell membrane.*

### Bile acid-activated macrophages promote biliary epithelial cell proliferation through integrin v6 upregulation following liver injury.

Guillot A, Guerri L, Feng D, Kim SJ, Ahmed YA, Paloczi J, He Y, Schuebel K, Dai S, Liu F, Pacher P, Kisseleva T, Qin X, Goldman D, Tacke F, Gao B.J Clin Invest. 2021 May 3;131(9):e132305. doi: 10.1172/JCI132305.PMID: 33724957 Free article. **Featured in Journal cover (see Science as Art section below).**

*In this study, we demonstrated that biliary epithelial cell injury induces cholestasis, monocyte recruitment, and induction of ITG6, which work together to promote BEC proliferation and therefore represent potential therapeutic targets for cholangiopathies.*

### Chemokines act as phosphatidylserine-bound "find-me" signals in apoptotic cell clearance.

Pontejo SM, Murphy PM.PLoS Biol. 2021 May 26;19(5):e3001259. doi: 10.1371/journal.pbio.3001259. Online ahead of print.PMID: 34038417

*This paper found that it is a general property of many chemokines to bind anionic phospholipids, including phosphatidylserine, a key marker of apoptotic cells and apoptotic bodies, which are extracellular vesicles released from apoptotic cells. When thymocytes undergo apoptosis, we found that they downregulate chemokine-binding glycosaminoglycans and upregulate phosphatidylserine, which binds endogenous chemokines, and release PS-binding chemokines on apoptotic bodies, which are chemotactic for macrophages, acting at G protein-couple chemokine receptors.*

### Promise and complexity of lupus mouse models.

Moore E, Reynolds JA, Davidson A, Gallucci S, Morel L, Rao DA, Young HA, Putterman C.Nat Immunol. 2021 Jun;22(6):683-686. doi: 10.1038/s41590-021-00914-4. PMID: 33972783

*This is a report of a virtual meeting held in December that covered the current status of mouse models of lupus and their relevance to human disease. This was a follow up to a previous meeting held 10 years earlier at the NIH. Data from top lupus research labs were presented in this meeting.*

### Lymphocytes sense antibodies through human FCRL proteins: Emerging roles in mucosal immunity.

Tolnay M.J Leukoc Biol. 2021 Apr 22. doi: 10.1002/JLB.4RU0221-102RR. Online ahead of print.PMID: 33884658 Review.

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*Fc receptor-like 3 (FCRL3), FCRL4, and FCRL5 are proposed to decode specific information from the immune complex which relates to "space" (mucosal versus systemic origin of IgA) and "time" (age of the IgG molecule). The potential contributions of FCRL3 and secretory IgA to the pathogenesis of autoimmune diseases are discussed.*

## Fibroblast tissue priming-not so nice to C you!

Afzali B, Kemper C.Immunity. 2021 May 11;54(5):847-850. doi: 10.1016/j.immuni.2021.04.010.PMID: 33979581

*Here we preview a recent publication proposing that local synovial fibroblasts perpetuate inflammation after priming through cell-intrinsic complement C3, which reprograms their bioenergetics and activates the inflammasome. This mechanism is proposed as the explanation for why relapses of inflammatory arthritis occur at previously affected sites. More broadly, accumulating evidence points to a critical role for dysregulation of cell-intrinsic complement production in human diseases.*

## Host-virus chimeric events in SARS-CoV2 infected cells are infrequent and artifactual.

Yan B*, Chakravorty S*, Mirabelli C*, Wang L, Trujillo-Ochoa JL, Chauss D, Kumar D, Lionakis MS, Olson MR, Wobus CE**, Afzali B**, Kazemian M**.J Virol. 2021 May 12:JVI.00294-21. doi: 10.1128/JVI.00294-21. Online ahead of print.PMID: 33980601
*joint first authors; ** joint last and corresponding authors

*Recent studies have reported the presence of host-virus chimeric (HVC) RNA in RNA-seq data from SARS-CoV2 infected cells and interpreted these findings as evidence of viral integration in the human genome as a potential pathogenic mechanism. Since SARS-CoV2 is a positive-sense RNA virus that replicates in the cytoplasm it does not have a nuclear phase in its life cycle. Thus, it is biologically unlikely to be in a location where splicing events could result in genome integration. Here we investigated the biological authenticity of host-virus chimeric (HVC) events. Our findings indicate that HVC events observed in RNA-sequencing libraries from SARS-CoV2 infected cells are extremely rare and are likely artifacts arising from either random template switching of reverse-transcriptase and/or sequence alignment errors. Therefore, the observed HVC events do not support SARS-CoV2 fusion to cellular genes and/or integration into human genomes.*

## Protection against SARS-CoV-2 infection by a mucosal vaccine in rhesus macaques.

Sui Y, Li J, Zhang R, Prabhu SK, Andersen H, Venzon D, Cook A, Brown R, Teow E, Velasco J, Greenhouse J, Putman-Taylor T, Campbell TA, Pessaint L, Moore IN, Lagenaur L, Talton J, Breed MW, Kramer J, Bock KW, Minai M, Nagata BM, Lewis MG, Wang LX, Berzofsky JA.JCI Insight. 2021 Apr 28;6(10):148494. doi: 10.1172/jci.insight.148494.PMID: 33908897.

*This shows that a mucosal SARS-CoV-2 spike S1 protein vaccine delivered intranasally can completely prevent replicating SARS-CoV2 in the lungs and provide better protection than a control IM in alum S1 vaccine despite inducing a lower level of neutralizing antibodies, correlated with induction of dimeric IgA and IFN-alpha, thus a different type of immune response, and can more rapidly clear input virus from the nasal mucosa. Thus, such a mucosal boost may be valuable to boost the current COVID-19 vaccines in use, which are all systemic vaccines.*

## SARS-CoV-2 spike protein suppresses ACE2 and type I interferon expression in primary cells from macaque lung bronchoalveolar lavage.

Sui, Y., J. Li, D. J. Venzon, and J. A. Berzofsky. Frontiers in Immunology, in press. 2021..

*This study investigates the effect of Spike S1 protein's binding to ACE2 on NHP.*

## Anti-PD-L1 therapy does not improve survival in a murine model of lethal Staphyloccocus aureus pneumonia.

Curran CS, Busch LM, Li Y, Xizhong C, Sun J, Eichacker PQ, Torabi-Parizi P.J Infect Dis. 2021 May 19:jiab274. doi: 10.1093/infdis/jiab274. Online ahead of print.PMID: 34009385.

*Despite increased expression of immune cell PD-L1 in a pneumonia model, PD-L1 inhibition did not improve survival. The time of antibody administration, dosing regimen, type of microbe, or the site of infection may affect the response.*

## Stay on Target: Reengaging Cancer Vaccines in Combination Immunotherapy.

Wolfson, B.; Franks, S.E.; Hodge, J.W. Vaccines 2021, 9, 509. https://doi.org/10.3390/vaccines9050509.

*This review summarizes ongoing clinical trials built upon the backbone of cancer vaccines, focusing on those that utilize multicombination (3+) immuno-oncology agents. These combinations and those yet to enter the clinic represent the future of cancer immunotherapy to effectively treat established tumors.*

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# CONGRATULATIONS

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## Anandani Nellan Appointed as Physician-Scientist Early Investigator

**Anandani Nellan, M.D., M.P.H., has been appointed as a Physician-Scientist Early Investigator in the Pediatric Oncology Branch (POB).**

**Prior to this appointment, Dr. Nellan served as an Assistant Professor at Children's Hospital Colorado. She is a pediatric neuro-oncologist specializing in pediatric hematology oncology and neuro-oncology. Her primary goal is to pioneer new immunotherapies for pediatric brain tumors, with a focus on preclinical, transitional studies in the laboratory.**

Dr. Anandani Nellan

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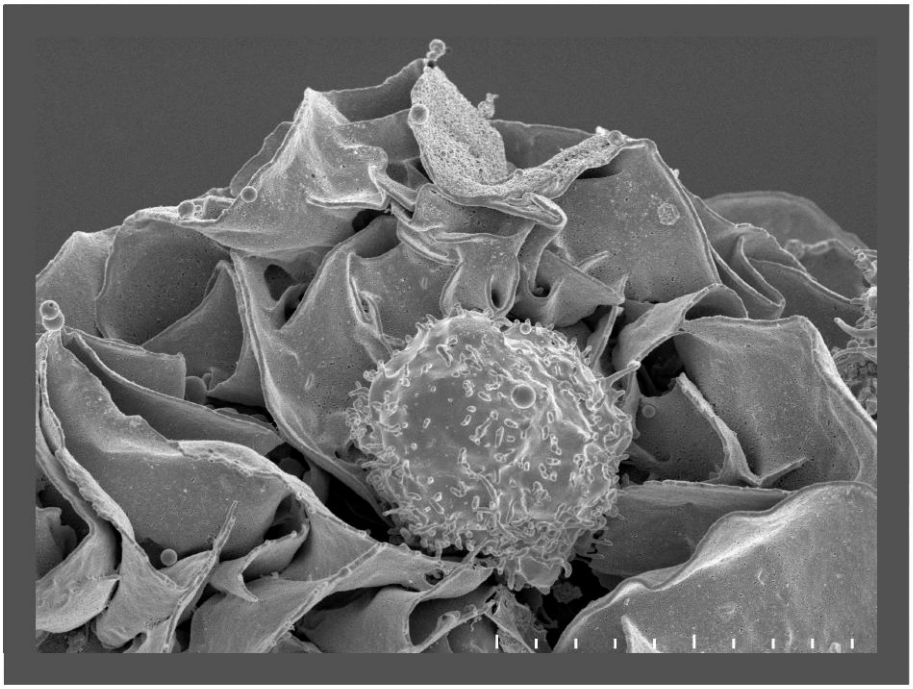
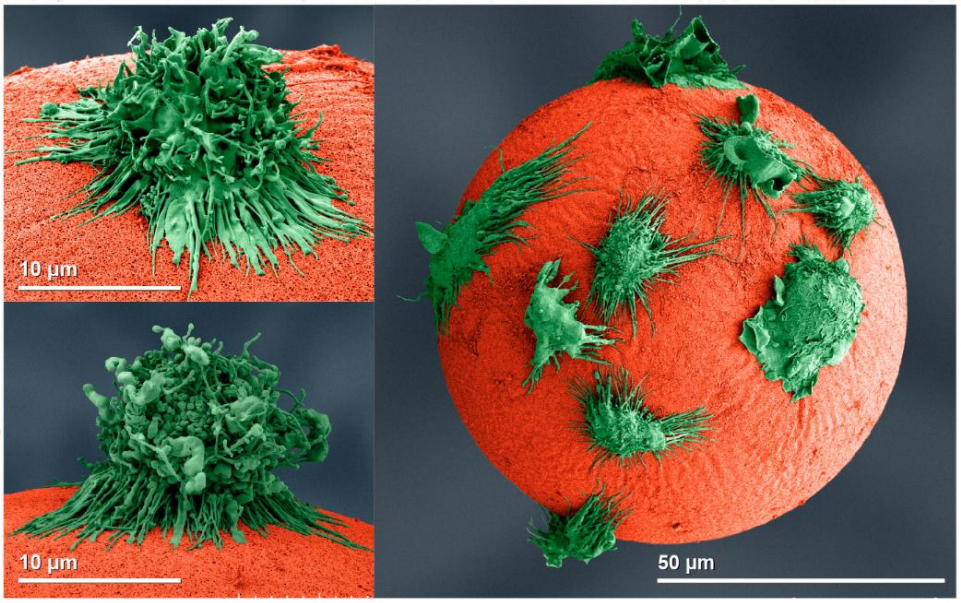
# T CELLS AND DENDRITIC CELL INTERACTION (EM IMAGES)



← The image depicts LPS-activated BMDC interacting with Ag-activated T cell.

This image shows that LPS-activated BMDCs interaction with Hist-CD40L bound to Ni-NTA agarose beads resulting in differential regulation of IL-12 and IL-23 in the presence or absence of IL-4. In addition, naïve T cells were unable to stimulate DCs for IL-12 production. Therefore, it appears that the induction of an IFN-γ (TH1) response is not solely dependent on decisions by DCs but rather on a complex interplay between the DCs and their local microenvironment. These findings suggest that perhaps we need to revisit the TH1/TH2 paradigm and the initiation of IFN-γ responses. →




**PUBLISHED IN:**

**Cutting Edge: Quantitative Determination of CD40L Threshold for IL-12 and IL-23 Production from Dendritic Cells**

Kaveh Abdi, Karen Laky, Kartika Padhan, Constantinos Petrovas, Jeff Skinner, Juraj Kabat, David W. Dorward, Joseph Brzostowski, Eric O. Long, Giorgio Trinchieri and Rajat Varma

J Immunol November 15, 2018, 201 (10) 2879-2884; DOI: https://doi.org/10.4049/jimmunol.1800721

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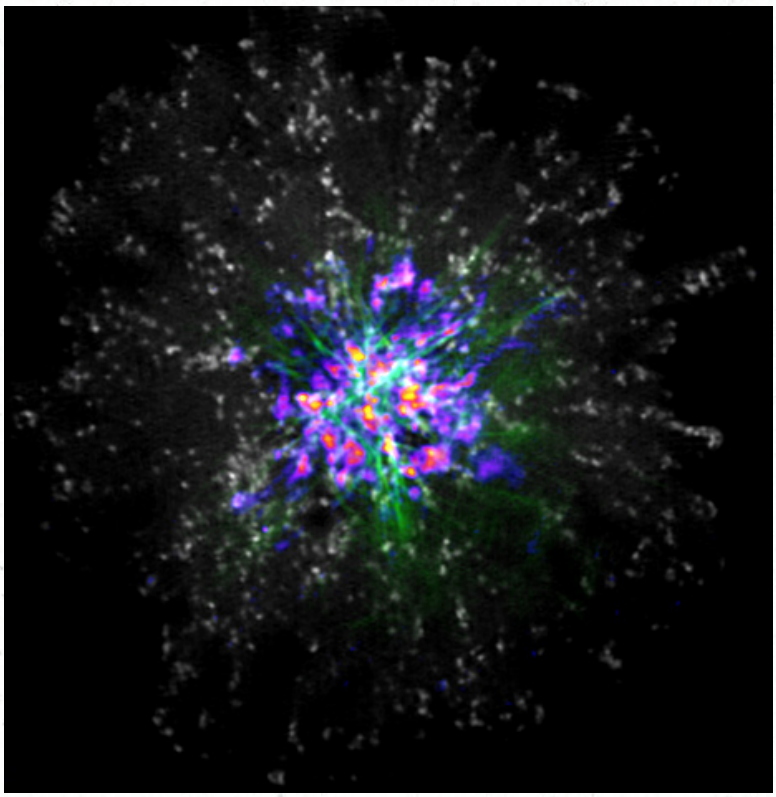
# ACTIVATED T CELL (TIRF-SIM IMAGE)



Activated T cell showing signaling microclusters (white), microtubules (green) and vesicles (fire).

**UNPUBLISHED IMAGE.**
Submitted by: Lakshmi Balagopalan (Laboratory of Cellular and Molecular Biology, NCI)



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# JCI COVER, MAY 2021 ISSUE


**FEATURING:**
Bile acid-activated macrophages promote biliary epithelial cell proliferation through integrin v6 upregulation following liver injury.

Guillot A, Guerri L, Feng D, Kim SJ, Ahmed YA, Paloczi J, He Y, Schuebel K, Dai S, Liu F, Pacher P, Kisseleva T, Qin X, Goldman D, Tacke F, Gao B.J Clin Invest. 2021 May 3;131(9):e132305. doi: 10.1172/JCI132305.PMID: 33724957

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# THE 2020 WILLIAM E. PAUL
# Best Paper in Cytokine Research Award

**presented by the NIH/FDA Cytokine Interest Group**

**Mini Symposium: June 10th, 2021, 10am-12pm**
**on webex**

**1st Place**

## Lindsey B. Rosen, NIAID

PhD Student, NIH-OxCam Program

Autoantibodies against type I IFNs in patients with life-threatening COVID-19
*Science 2020*

**2nd Place *ex aequo***

## Zuojia Chen, NCI

Postdoctoral Fellow

Interleukin-33 Promotes Serotonin Release from Enterochromaffin Cells for Intestinal Homeostasis
*Immimmunity 2021*

**2nd Place *ex aequo***

## Wai Po Chong, NEI

Associate Professor, Sun Yat-Sen University, China

The Cytokine IL-17A Limits Th17 Pathogenicity via a Negative Feedback Loop Driven by Autocrine Induction of IL-24
*Immunity 2020*

**3rd Place *ex aequo***

## Junji Xu, NIDCR

Dentist, Beijing Stomatology Hospital

The Cytokine TGF-β Induces Interleukin-31 Expression from Dermal Dendritic Cells to Activate Sensory Neurons and Stimulate Wound Itching *Immunity 2020*

**3rd Place *ex aequo***

## Sang Hun Lee, NIAID

Staff Scientist

M2-like, dermal macrophages are maintained via IL-4/CCL24–mediated cooperative interaction with eosinophils in cutaneous leishmaniasis
*Science Immunology 2020*