NIH-FDA IIG NEWSLETTER

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

JUNE 2021

PUBLICATIONS

Antigenic cartography reveals complexities of genetic determinants that lead to antigenic differences among pandemic GII.4 noroviruses.

Kendra JA, Tohma K, Ford-Siltz LA, Lepore CJ, Parra GI.Proc Natl Acad Sci U S A. 2021 Mar 16;118(11):e2015874118. doi: 10.1073/pnas.2015874118. PMID: 33836574

Using the largest panel of GII.4 noroviruses and cartography analyses we demonstrated a minimum threshold of coevolving amino acid changes at multiple antigenic sites needed for meaningful antigenic differences. This contrast to other viruses, like influenza, that single mutations at immunodominant sites could results in substantial antigenic changes.

Understanding the relationship between norovirus diversity and immunity.

A Ford-Siltz L, Tohma K, I Parra G.Gut Microbes. 2021 Jan-Dec;13(1):1-13. doi: 10.1080/19490976.2021.1900994. PMID: 33783322

This study provides a comprehensive review on the relationship between human norovirus genetic and antigenic diversity and immune correlates of protection that should be considered for the development of cross-protective norovirus vaccines.

Notch signaling and efficacy of PD-1/PD-L1 blockade in relapsed small cell lung cancer.

Roper N, Velez MJ, Chiappori A, Kim YS, Wei JS, Sindiri S, Takahashi N, Mulford D, Kumar S, Ylaya K, Trindade C, Manukyan I, Brown AL, Trepel JB, Lee JM, Hewitt S, Khan J, Thomas A.Nat Commun. 2021 Jun 23;12(1):3880. doi: 10.1038/s41467-021-24164-y.PMID: 34162872

Immune checkpoint blockade benefits only a small subset of patients with small cell lung cancer. In this study, we performed immunogenomic profiling of tumor samples from relapsed SCLC patients treated with immunotherapy to identify Notch activation as a determinant of increased intrinsic tumor immunity, paving the way for more effective application of immunotherapy in SCLC

Molecular chaperone RAP interacts with LRP1 in a dynamic bivalent mode and enhances folding of ligand-binding regions of other LDLR family receptors.

Marakasova E, Olivares P, Karnaukhova E, Chun H, Hernandez NE, Kurasawa JH, Hassink GU, Shestopal SA, Strickland DK, Sarafanov AG.J Biol Chem. 2021 May 29;297(1):100842. doi: 10.1016/j.jbc.2021.100842. Online ahead of print.PMID: 34058195

This work is focused on dissecting the molecular mechanism of interaction of LDLR family receptors with its ligands (for example, LRP1 and RAP).

Tumor Extrinsic Factors Mediate Primary T-DM1 Resistance in HER2-Positive Breast Cancer Cells.

Endo Y, Wu WJ. 2021. Cancers 13, no. 10: 2331. https://doi.org/10.3390/cancers13102331.

Using Matrigel matrix as a model of the tumor microenvironment, we find that the extrinsic factors contribute to the primary resistance of HER2-positive breast cancer cells to T-DM1. This finding provides an opportunity to develop a novel therapeutic strategy to overcome therapeutic resistance to T-DM1.

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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. eCollection 2021 May.PMID: 34038417

We found that anionic phospholipids, particularly phosphatidylserine (PS) and cardiolipin, constitute a third class of high affinity chemokine binding site on cells, the others being G protein-coupled receptors and glycosaminoglycans. PS is externalized on the plasma membrane of apoptotic cells and exosomes where it binds many chemokines. Investigating the significance of this, we found that PS-bound chemokines serve as find-me signals on apoptotic vesicles acting at cognate chemokine receptors on phagocytes, suggesting a chemokine-dependent mechanism for apoptotic cell clearance.

Cytokines: From Clinical Significance to Quantification.

Liu C, Chu D, Kalantar-Zadeh K, George J, Young HA, Liu G. Advanced Science (Weinheim, Baden-wurttemberg, Germany). 2021 Jun:e2004433. DOI: 10.1002/advs.202004433

In this review, various quantification platforms for high-sensitivity and reliable measurement of cytokines in different scenarios are discussed, and commercially available cytokine assays are compared. In addition, a discussion of challenges in the development and advancement of technologies for cytokine quantification that aim to achieve real-time multiplex cytokine analysis for point-of-care situations applicable for both biomedical research and clinical practice are discussed.

CAR T cells targeting tumor-associated exons of glypican 2 regress neuroblastoma in mice.

Li N, Torres M, Spetz MR, Wang R, Peng L, Tian M, Dower CM, Nguyen R, Sun M, Tai CH, Val ND, Cachau R, Wu X, Hewitt SM, Kaplan RN, Khan J, Croix B, Thiele CJ, and Ho M. Cell Reports Medicine,Volume 2, Issue 6, 2021, https://doi.org/10.1016/j.xcrm.2021.100297

Using RNA sequencing (RNA-seq) analysis, we identify tumor-associated exons of glypican 2 (GPC2). We isolate a monoclonal antibody CT3 that specifically binds to these exons, and visualize the complex structure of CT3 and GPC2 by electron microscopy. The CT3-derived CAR T cells regress neuroblastoma in mice.

Advances in immunotherapeutic targets for childhood cancers: A focus on glypican-2 and B7-H3.

Li N, Spetz MR, Li D, Ho M.Pharmacol Ther. 2021 Jul;223:107892. doi: 10.1016/j.pharmthera.2021.107892. Epub 2021 May 14.PMID: 33992682 Review.

In this review, we summarize the immunotherapeutic agents that have been approved for treating childhood cancers and provide an updated review of molecules expressed by pediatric cancers that are under study or are emerging candidates for future immunotherapies. Glypican 2 (GPC2) and B7-H3 (CD276) are two cell surface antigens that are expressed by a variety of pediatric tumors such as neuroblastoma and potentially can have a positive impact on the treatment of pediatric cancers in the cliniC.

Extracellular Acidity Reprograms Macrophage Metabolism and Innate Responsiveness.

Jiang W, Le J, Wang PY, Cheng X, Smelkinson M, Dong W, Yang C, Chu Y, Hwang PM, Munford RS, Lu M.J Immunol. 2021 Jun 9:ji2100014. doi: 10.4049/jimmunol.2100014. Online ahead of print.PMID: 34108259.

Low extracellular pH rendered macrophages less inflammatory and less able to phagocytose bacteria yet the cells regained basal energy production and proinflammatory responsiveness when neutral pHe was restored 48 hrs later. Macrophage responses to low interstitial pH may contribute to the reversible organ hypofunction and immunoparalysis noted in many patients with sepsis.

In Situ Characterization of Human Lymphoid Tissue Immune Cells by Multispectral Confocal Imaging and Quantitative Image Analysis; Implications for HIV Reservoir Characterization.

Moysi E, Del Rio Estrada PM, Torres-Ruiz F, Reyes-Terán G,. Koup RA and Petrovas C. Frontiers in Immunology, 12, 2058.

A paper describing the development and optimization of eight multispectral confocal microscopy immunofluorescence panels designed for in depth characterization and profiling of immune cells in formalin-fixed paraffin-embedded (FFPE) human lymphoid tissue samples.

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CCL17-producing cDC2s are essential in end-stage lupus nephritis and averted by a parasitic infection.

Amo L, Kole HK, Scott B, Qi CF, Wu J, Bolland S.J Clin Invest. 2021 Jun 1;131(11):e148000. doi: 10.1172/JCI148000. PMID: 34060489

Infection with Malaria parasite protects from end-stage lupus nephritis without altering systemic autoimmunity. This long-term protection is brought about by the inhibition of kidney infiltrating CCL17-producing cDC2s with BM origin.

NHS-IL12, a tumor-targeting immunocytokine [review].

Greiner JW, Morillon II YM, Schlom J. Immunotargets & Therapy. 2021 May 27;10:155-169. eCollection 2021.

This review of preclinical and early clinical data presents a compelling argument for the continued development of NHS-IL12, a novel immunocytokine designed for delivery of IL-12 to the tumor microenvironment (TME). Tumor-targeting of IL-12 via NHS-IL12 initiates a change from an immunosuppressive to an immunopermissive TME which, in turn, can initiate antitumor effects alone and/or assist in the antitumor efficacy of other cancer therapeutics.

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CONGRATULATIONS TO DR. HOWARD YOUNG FOR RECEIVING THE 2021 ICIS MENTORSHIP AWARD!

Our own Dr. Young is the first recipient of the ICIS mentorship award! The NIH-FDA committee and the entire community would like to congratulate him on this award as no one deserves it more than him. This award recognizes individuals who have made significant and sustained contributions to the career development of trainees and to the profession through outstanding mentorship.

Dr. Howard Young

Dr. Howard Young is a Senior Investigator in the Laboratory of Cancer Immunometabolism, Center for Cancer Research, National Cancer Institute in Frederick, MD. His research focuses on the regulation and characterization of cytokine gene expression with a special emphasis on interferons. Over four decades, Dr. Young has trained and mentored many post-docs and post-bacs who now hold significant leadership positions.

Dr. Young has received NCI and NIH mentorship awards for his mentorship and leadership role in establishing the Werner H Kristen High-School Summer internship program. Dr. Werner Kristen, a previous NCI Frederick Director, started an internship program in 1989 that introduces lab science to high school seniors (around 30-40 students/year) and this program has been a tremendous success with over 1000 students trained through the program. Dr. Young has also significantly invested time and effort in training post-bacs, many of whom have gone onto successful careers in science and medicine.

Dr. Young is a 3-time recipient of the NIH outstanding mentor award and is a recipient of the mentorship award from the Center for Cancer Research Women Scientists Association. He has chaired both the NIH Immunology Interest Group and Cytokine Interest Group twice. He has served on many ICIS committees, was President of the International Society for Interferon and Cytokine Research, and the editor of the ICIS/ISICR newsletter since its inception.

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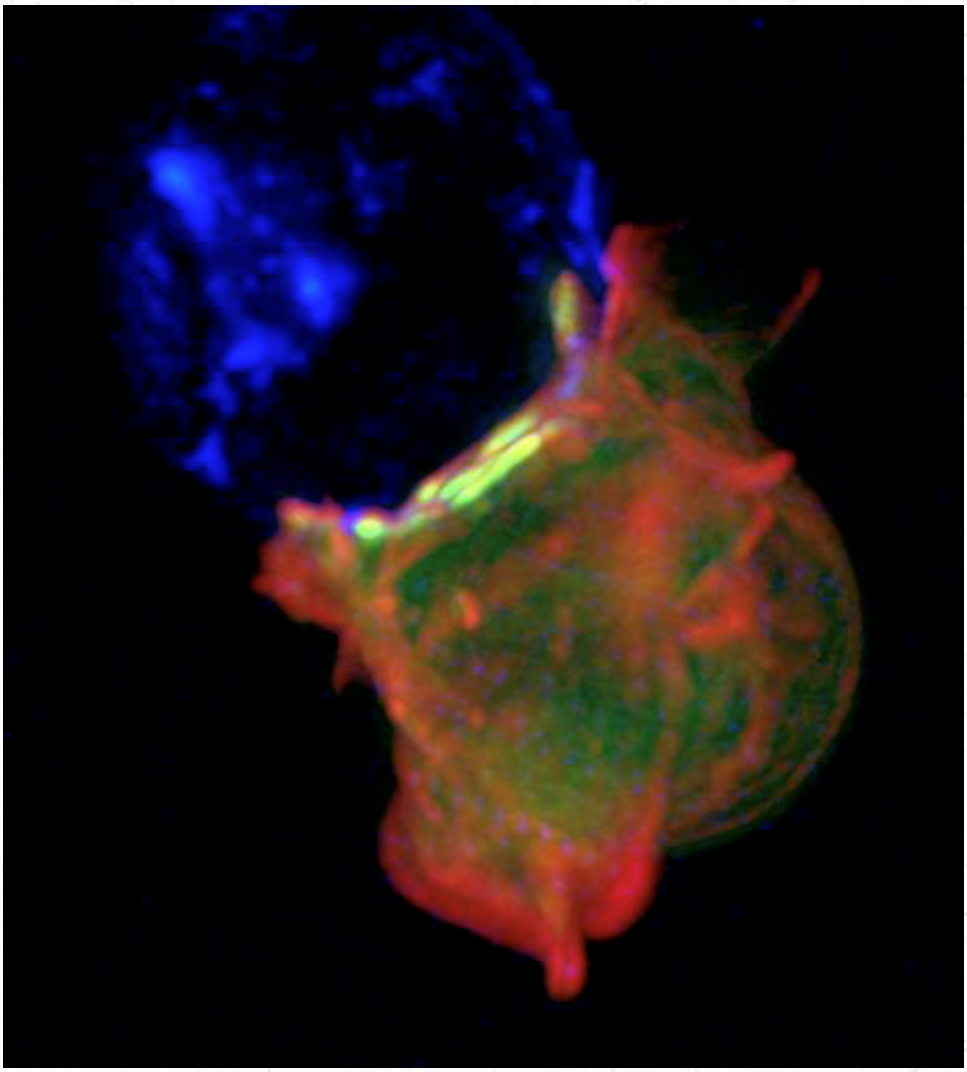
IMMUNOLOGICAL SYNAPSE



A lattice light sheet image of a T cell expressing T cell receptor (TCR-zeta) and a proximal kinase (ZAP70) forming a synapse with a B cell (blue). You can see receptor and kinase clusters at the synapse.

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

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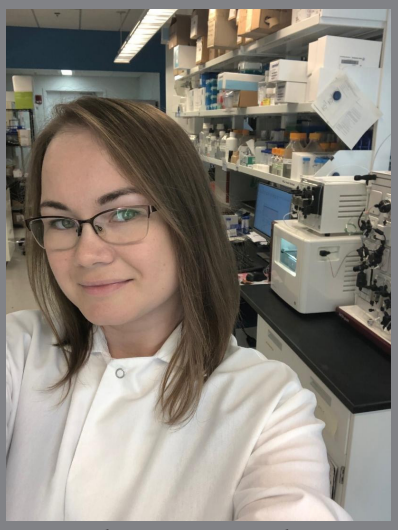
CONGRATULATIONS!

Dr. Ekaterina Marakasova

Dr. Marakasova is appointed as scientific reviewer at Center for Devices and Radiological Health CDRH, FDA. She joined FDA as a scientific reviewer to review immunology In vitro diagnostics (IVD) devices.



Dr. Ekaterina Marakasova

Before moving on to this position, Ekaterina worked as an ORISE Research Fellow in Dr. Sarafanov's laboratory at OTAT/CBER, FDA (Office of Tissues and Advanced Therapies/ Center for Biologics Evaluation and Research). Her work from her time was recently published in J Bio Chem and is highlighted in the publications section of this newsletter.

Ekaterina graduated with B.S. in Biology (2008) and M.S. in Genetics (2009) from Ivan Franko National University (Ukraine). In 2011 she joined George Mason University (Virginia) as a Fulbright fellow. In 2018 she earned a Ph.D. in molecular and cellular biology from George Mason University (Virginia), and the same year she joined OTAT/CBER (FDA) as an ORISE Research Fellow. In 2020 Ekaterina joined CDRH/OPEQ/OHT7/ DIHD, FDA (Center for Devices and Radiological Health/ Office of Product Evaluation and Quality/ Office of Health Technology 7/ Division of Immunology & Hematology Devices) as a scientific reviewer.