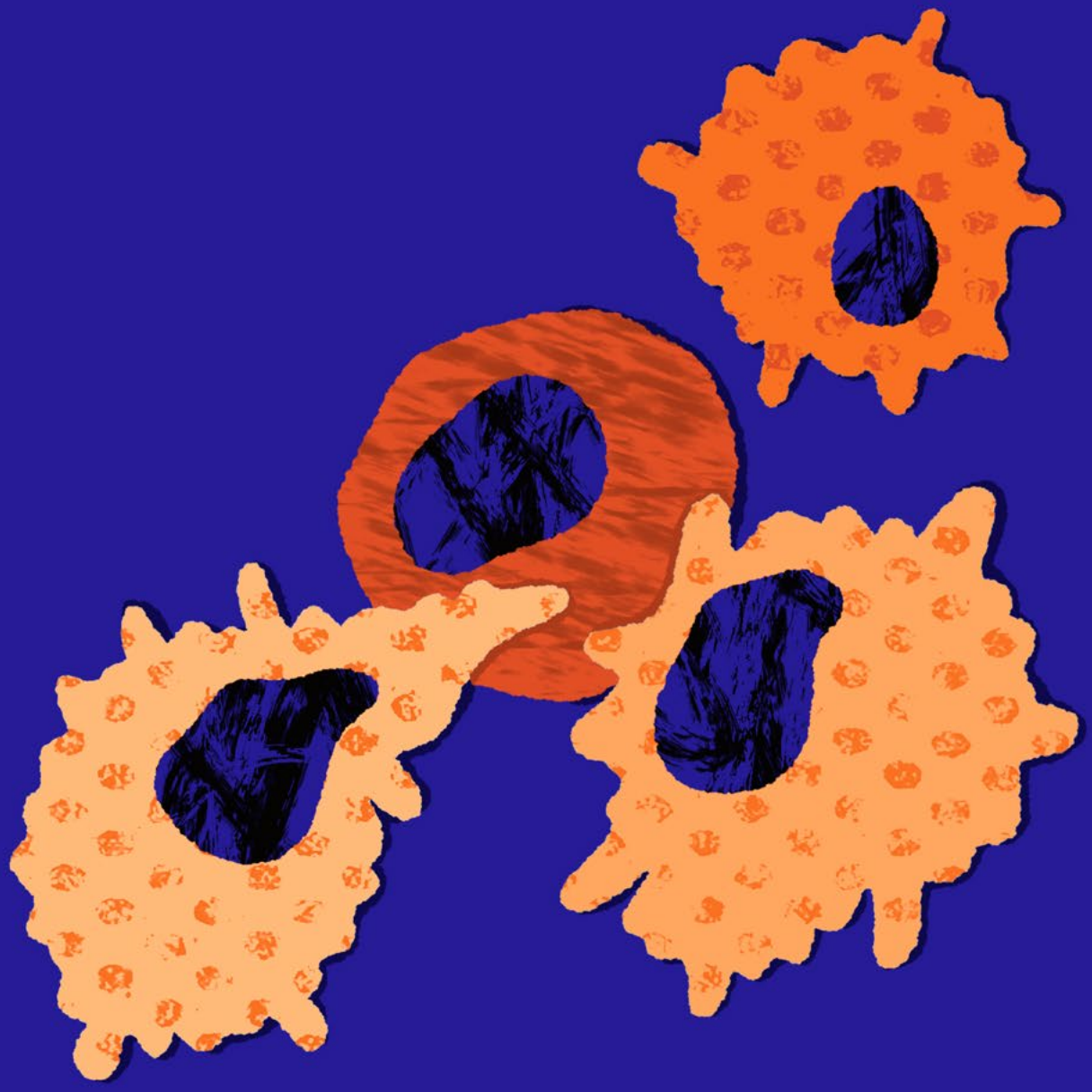
JEM Journal of Experimental Medicine



2019: THE YEAR IN EXPERIMENTAL MEDICINE

WHY SUBMIT TO JEM?

JEM Journal of Experimental Medicine

92% OF INVITED REVISIONS ARE ACCEPTED

INITIAL DECISION IN 6 DAYS

TIME IN PEER REVIEW 38 DAYS

*Median 2019

FORMAT NEUTRAL

You may submit your papers in ANY format.

TRANSFER POLICY

We welcome submissions that include reviewer comments from another journal. You may also request manuscript transfer between Rockefeller University Press journals, and we can confidentially send reviewer reports and identities to another journal beyond RUP.

FAIR AND FAST

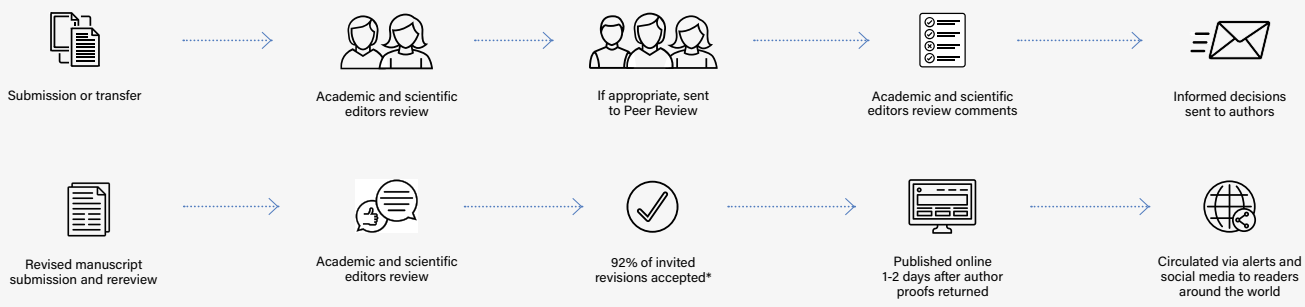
We limit rounds of revision, and we strive to provide clear, detailed decisions that illustrate what is expected in the revisions. Articles appear online one to two days after author proofs are returned.

OPEN ACCESS OPTIONS

Our options include Immediate Open Access (CC-BY) and open access six months after publication (CC-BY-NC-SA).

An Editorial Process Guided by Your Community

At *JEM*, all editorial decisions on research manuscripts are made through collaborative consultation between professional scientific editors and the academic editorial board.



2019: THE YEAR IN EXPERIMENTAL MEDICINE

At the beginning of 2020, the start of a new decade, the *Journal of Experimental Medicine* (*JEM*) is proud to present our annual Year in Experimental Medicine collection to highlight some of the articles that were of greatest interest to our readers last year. The top 10 papers are selected by the editorial team and are based, in part, on the number of requests for PDF and full-text HTML versions of an article in the first three months after publication. These studies highlight the full breadth of *JEM*'s scope and our long-standing interest in original findings in disease pathogenesis.

We would like to thank our authors for contributing to *JEM*. It is our privilege to publish ground-breaking studies that broaden knowledge in immunology, host–pathogen interaction, cancer biology, cardiovascular biology, neuroscience, and other areas relevant to disease pathogenesis. In 2019, we celebrated the recipients of the Albert Lasker Basic Medical Research Award with a collection of *JEM* studies from Max D. Cooper (Emory University) and Jacques Miller (Walter and Eliza Hall Institute of Medical Research) that revolutionized our understanding of the adaptive immune system. Find this collection and many others at https://rupress.org/JEM/collections.

We are also grateful to our reviewers. See page 15 for a full list of those who contributed their time and expertise to ensure the publication of quality science in *JEM* in 2019.

Last but not least, we would like to thank our readers for their interest and continued support for *JEM*. We hope you will enjoy reading this collection.

Brochure articles by Ben Short, PhD

Design by Christine Candia

Cover art by Laura Avivar

On the cover Anti-tumor immune response. T cells attacking a cancer cell.

CONNECT WITH JEM

@JExpMed
Journal of Experimental Medicine
@rockefeller_university_press
jem@rockefeller.edu

www.jem.org

JEM Journal of Experimental Medicine

Print ISSN 0022-1007
Online ISSN 1540-9538

Rockefeller University Press

$CD4^+$ RESIDENT MEMORY T CELLS MEDIATE LOCAL IMMUNE RESPONSE

Study reveals that CD4 T_{RM} cells play a major role in immunosurveillance and local responses to reinfection

Naïve T cells largely patrol the body by circulating through secondary lymphoid organs. In contrast, $CD8^+$ memory T cells that have previously been exposed to their cognate antigen are abundant enough to permanently station themselves in various nonlymphoid tissues, becoming resident memory T cells (T_{RM}) that can mediate local immunosurveillance and detect any reinfections.

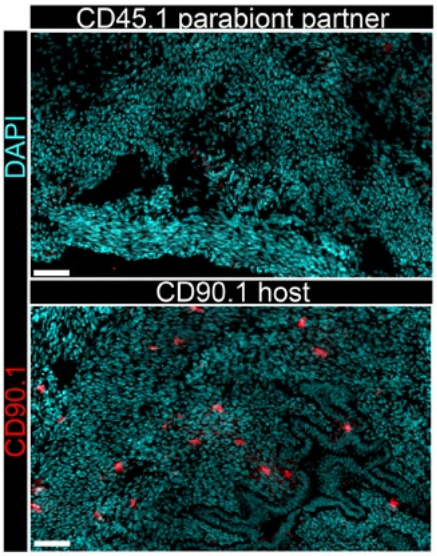
"The extent to which residence contributes to global memory $CD4^+$ T cell surveillance is less clear," explains David Masopust of the University of Minnesota. "There have been fewer studies on the surveillance patterns of $CD4^+$ T cells, and they have produced varied conclusions or indicated a more complex situation."

Masopust and colleagues, including first author Lalit Beura, performed a comprehensive analysis of the $CD4^+$ memory T cells formed in mice exposed to lymphocytic choriomeningitis virus (LCMV). $CD4^+$ memory T cells recognizing this virus were broadly distributed in both lymphoid and nonlymphoid tissues, as well as in the blood. In the case of nonlymphoid tissues, most $CD4^+$ memory T cells appeared to be resident cells conducting local immunosurveillance. These $CD4^+$ T_{RM} cells were reactivated upon exposure to further LCMV antigen, triggering a rapid, local immune response by components of both the innate and adaptive immune systems. The researchers saw a similarly prominent role for $CD4^+$ T_{RM} cells in mice exposed to an array of natural pathogens.

Beura et al. found that $CD4^+$ T_{RM} cells share many phenotypic characteristics with $CD8^+$ T_{RM} cells residing in the same tissue. Transcriptional profiling revealed that, though $CD4^+$ T_{RM} cells from different tissues have distinct gene expression patterns, they share a common transcriptional signature that distinguishes them from circulating $CD4^+$ T cells. Remarkably, a similar residence signature can also be found in $CD8^+$ T_{RM} cells residing in diverse tissues.

"Taken together, these results reveal a shared gene signature of tissue residence that transcends anatomical location and T cell lineage," says Beura. "We propose at least three axes of differentiation for memory T cells: one driven by the specific tissue microenvironment, one driven by lineage ($CD4^+$ vs. $CD8^+$), and one coupled to whether the cells are tissue resident or recirculating."

"Our paper highlights the dominance of resident-mediated $CD4^+$ T cell immunosurveillance, and indicates that further studies of $CD4^+$ T_{RM} biology will be important to our understanding of immune responses throughout the body," Masopust says.



Staining of mucosal tissue from two mice parabiotically connected for several weeks after LCMV infection shows that $CD4^+$ memory T cells (red) remain in their original host and do not spread to the other animal, indicating that they are tissue-resident rather than circulating cells.
Credit: Beura et al., 2019

RESEARCHER DETAILS

Lalit K. Beura
Postdoctoral Associate; University of Minnesota; (Currently an Assistant Professor at Brown University)

David Masopust
Professor; University of Minnesota;
masopust@umn.edu

ORIGINAL PAPER

Beura, L.K., N.J. Fares-Frederickson, E.M. Steinert, M.C. Scott, E.A. Thompson, K.A. Fraser, J.M. Schenkel, V. Vezys, and D. Masopust. 2019. $CD4^+$ resident memory T cells dominate immunosurveillance and orchestrate local recall responses. *J. Exp. Med.* 216:1214–1229.
https://doi.org/10.1084/jem.20181365

A NOVEL T CELL SUBSET CONTROLS IgE RESPONSES IN HUMANS

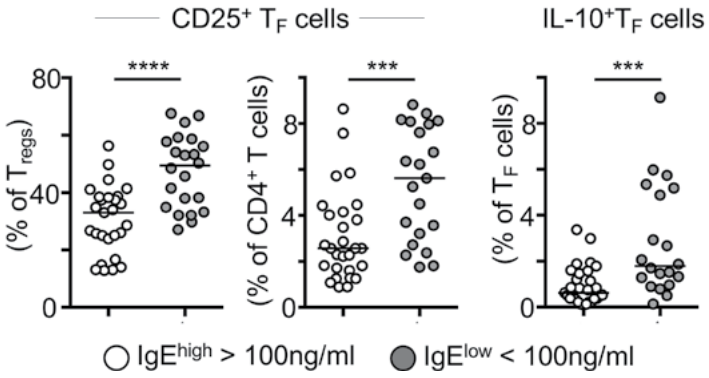
A population of regulatory T cells in the follicles of human tonsils may prevent allergies by reducing IgE production

Antibody responses must be carefully calibrated to ensure maximal protection against pathogens while avoiding excessive inflammation, autoimmune reactions, or, in the case of IgE-mediated antibody responses, allergic reactions and anaphylaxis. In the follicles of secondary lymphoid organs, the differentiation of antibody-producing B cells is facilitated by follicular helper T (T_{FH}) cells. At least in mice, this activity is counteracted by follicular regulatory T (T_{FR}) cells that can reduce antibody production by suppressing both T_{FH} and B cell function. But whether a similar population of repressive cells exists in humans is unclear.

"In an effort to identify the human equivalent of mouse T_{FR} cells, we examined cells in the most accessible human secondary lymphoid tissue: the tonsils," says Carola Vinuesa, a professor at The Australian National University in Canberra.

Vinuesa and colleagues, including first author Pablo Cañete, identified a population of CD25⁺ follicular T (T_F) cells in human tonsils that secrete abundant amounts of IL-10, a cytokine expressed by mouse T_{FR} cells. Unlike mouse T_{FR} cells, however, these human CD25⁺ T_F cells did not express the transcription factor FOXP3, which is generally considered to be a master regulator of regulatory T cell function.

Yet the cells expressed other crucial markers of regulatory T cells and were able to suppress T cell proliferation, suggesting they could perform a regulatory function. Moreover, RNA sequencing revealed that, aside from FOXP3 expression, human CD25⁺ T_F cells had a similar transcriptional profile to mouse T_{FR} cells.



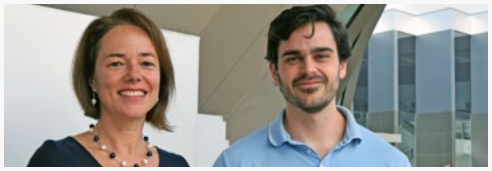
The frequency of IL-10-producing CD25⁺ T_F cells in the tonsils is higher in children with low serum IgE levels than in children with high IgE titers.
Credit: Cañete et al., 2019

The researchers determined that CD25⁺ T_F cells can suppress T_{FH} function in vitro. And, though they moderately promote the proliferation and differentiation of B cells, CD25⁺ T_F cells repress class switching to IgE in an IL-10–dependent manner. Accordingly, Vinuesa and colleagues found that children with high numbers of IL-10–producing CD25⁺ T_F cells in their tonsils had lower levels of IgE in their blood, whereas those with lower CD25⁺ T_F cell numbers displayed high IgE titers.

"Because this T cell subset is particularly abundant in the tonsils, which are constantly exposed to inhaled and ingested molecules, we think that these cells may be important to prevent IgE-mediated allergic reactions to harmless foreign antigens," Cañete explains.

"We therefore predict that deficiencies in this T cell subset could underpin susceptibility to allergic and anaphylactic reactions induced by inhaled and ingested antigens," Vinuesa adds. "Should this be the case, our findings may open up new avenues for boosting CD25⁺ T_F cells to reduce the risk of allergy."

RESEARCHER DETAILS



Carola G. Vinuesa
Professor; The John Curtin School of Medical Research; The Australian National University;
carola.vinuesa@anu.edu.au

Pablo F. Cañete
Postdoctoral Fellow; The John Curtin School of Medical Research; The Australian National University

ORIGINAL PAPER

Cañete, P.F., R.A. Sweet, P. Gonzalez-Figueroa, I. Papa, N. Ohkura, H. Bolton, J.A. Roco, M. Cuenca, K.J. Bassett, I. Sayin, E. Barry, A. Lopez, D.H. Canaday, M. Meyer-Hermann, C. Doglioni, B. Fazekas de St Groth, S. Sakaguchi, M.C. Cook, and C.G. Vinuesa. 2019. Regulatory roles of IL-10–producing human follicular T cells. *J. Exp. Med.* 216:1843–1856.
https://doi.org/10.1084/jem.20190493

PATIENTS WITH IL-6 RECEPTOR DEFICIENCY

Loss-of-function mutations in human *IL6R* lead to recurrent infections, eczema, and abnormal inflammatory responses

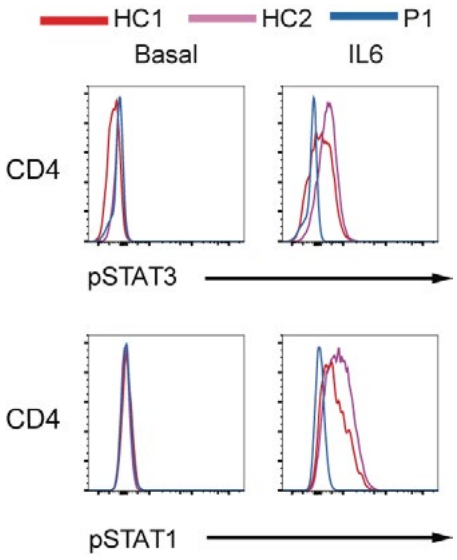
The proinflammatory cytokine IL-6 induces cell growth and proliferation by binding to its receptor, IL-6R, forming a complex that can associate with the membrane glycoprotein GP130 and activate a signaling pathway that leads to the nuclear import of STAT transcription factors. Excess IL-6 causes a variety of inflammatory diseases, and tocilizumab, an antibody that blocks the IL-6 receptor, is an effective treatment for several of these conditions, including rheumatoid arthritis.

"However, while the consequences of excessive IL-6 signaling in humans have been well established, the consequences of impairment have been more elusive," says James Thaventhiran, a research scientist at the Medical Research Council Toxicology Unit, University of Cambridge. Patients with loss-of-function mutations in the genes encoding GP130 or STAT3 are susceptible to recurrent infections, are prone to eczema and other allergic disorders, and suffer from a variety of skeletal and connective tissue abnormalities. But, because GP130 and STAT3 are also components of several other signaling pathways, the contribution of diminished IL-6 signaling to these symptoms is unclear.

Thaventhiran and colleagues, including co-corresponding authors Kaan Boztug of the Ludwig Boltzmann Institute for Rare and Undiagnosed Diseases, and Joshua Milner of the National Institute of Allergy and Infectious Diseases (now at Columbia University), identified two unrelated patients with loss-of-function mutations in the gene encoding IL-6R. Both patients suffered from recurrent bacterial infections of the skin and lung that were accompanied by abnormally low levels of inflammation (including reduced levels of the IL-6-induced acute-phase protein CRP). The patients also displayed elevated IgE levels and suffered from allergic diseases including eczema.

"Aspects of these patients' clinical phenotype—particularly their elevated IgE, atopic dermatitis, and susceptibility to staphylococcal infections—are shared by patients with mutations in the genes encoding STAT3, GP130, and ZNF341 (a transcription factor that regulates STAT3 levels)," says Boztug.

The patients with *IL6R* mutations did not, however, show any skeletal or connective tissue defects. "Our results therefore clarify the contribution of deficient IL-6 signaling to the phenotype of patients with loss-of-function mutations in *GP130, STAT3*, or *ZNF34*," says Milner. "This may indicate novel therapeutics for the alleviation of some of these patients' symptoms, such as using recombinant soluble IL-6R to increase the presentation of IL-6 to GP130. It is surprising, though, that a receptor which can contribute to so many other types of inflammatory disorders actually causes allergic inflammation when absent."



Fluorescence histograms show that, compared with cells from two healthy controls (HC1 and HC2), IL-6-induced phosphorylation of STAT3 and STAT1 is absent in the CD4⁺ T cells of a patient with a null mutation in *IL6R* (P1). Credit: Spencer et al., 2019

"In addition, the patients we describe in our report alerts us to the potential toxicity of tocilizumab or other drugs targeting the IL-6 receptor," Thaventhiran says.

RESEARCHER DETAILS

Kaan Boztug
Director, Ludwig Boltzmann Institute for Rare and Undiagnosed Diseases; Scientific Director, St. Anna Children's Cancer Research Institute;
kaan.boztug@rud.lbg.ac.at

Joshua D. Milner
Chief, Laboratory of Allergic Diseases; National Institute of Allergy and Infectious Diseases, National Institutes of Health;
joshua.milner@nih.gov

James E.D. Thaventhiran
Rutherford Fellow; Medical Research Council Toxicology Unit; University of Cambridge;
jedt2@mrc-tox.cam.ac.uk

ORIGINAL PAPER

Spencer, S., S. Köstel Bal, W. Egner, H. Lango Allen, S.I. Raza, C.A. Ma, M. Gürel, Y. Zhang, G. Sun, R.A. Sabroe, D. Greene, W. Rae, T. Shahin, K. Kania, R.C. Ardy, M. Thian, E. Staples, A. Pecchia-Bekkum, W.P.M. Worrall, J. Stephens, M. Brown, S. Tuna, M. York, F. Shackley, D. Kerrin, R. Sargur, A. Condliffe, H.N. Tipu, H.S. Kuehn, S.D. Rosenzweig, E. Turro, S. Tavaré, A.J. Thrasher, D.I. Jodrell, K.G.C. Smith, K. Boztug, J.D. Milner, and J.E.D. Thaventhiran. 2019. Loss of the interleukin-6 receptor causes immunodeficiency, atopy, and abnormal inflammatory responses. *J. Exp. Med.* 216:1986–1998.
https://doi.org/10.1084/jem.20190344

ZIKA-ASSOCIATED BIRTH DEFECTS MAY DEPEND ON MOTHER'S IMMUNE RESPONSE

Risk of developing fetal microcephaly is linked to the types of antibody produced by pregnant mothers in response to Zika infection

The Zika virus is spread by mosquitoes in tropical and subtropical regions, and, in most adults, the symptoms of infection, if any, are fairly mild. But the widespread Zika outbreak in Brazil in 2015–2016 revealed that infection during pregnancy can cause a wide range of fetal abnormalities, with microcephaly occurring in around 5% of live births by Zika-infected mothers.

"Why some Zika virus–infected pregnant women deliver apparently healthy newborns while others have babies with microcephaly is unknown," says Davide Robbiani from The Rockefeller University in New York.

Various factors have been proposed to increase the risk of microcephaly, including previous exposure to viruses that are similar to Zika, such as dengue virus or West Nile virus. Antibodies generated by the body's immune system to combat these viruses may recognize the Zika virus but, instead of neutralizing it, help it to enter the mother's cells and possibly cross the placenta to infect the unborn fetus.

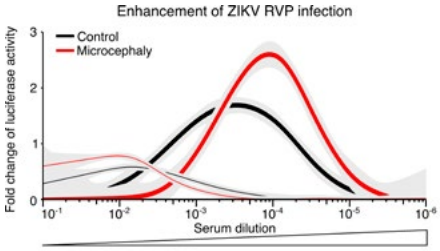
Robbiani and colleagues, including co-senior author Michel Nussenzweig, worked with researchers and physicians in Brazil to analyze blood samples collected during the 2015–2016 outbreak from Zika-infected mothers who had given birth to either apparently healthy or microcephalic children.

Through a series of laboratory tests, the researchers saw no significant differences in the antibodies produced against dengue or other Zika-related viruses, suggesting that prior exposure to these pathogens does not increase the risk of Zika-associated birth defects.

However, when Robbiani and colleagues analyzed the activity of antibodies produced against the Zika virus itself, they saw several differences in the antibodies produced by the mothers of babies with microcephaly. Antibodies from these mothers were actually more effective at neutralizing the Zika virus than the antibodies produced by mothers of healthy newborns. In addition, in a different assay, these antibodies showed an enhanced ability to boost the entry of Zika virus into human cells grown in the laboratory.

The researchers confirmed their findings in macaques infected with the Zika virus. Pregnant monkeys that produced more of the antibodies capable of enhancing viral entry into cells were more at risk of giving birth to babies suffering from Zika-induced brain damage.

"Though our results only show a correlation at this point, they suggest that antibodies may be implicated in Zika fetal disease," Robbiani says. "Antibodies may exist that, instead of protecting, enhance the risk of microcephaly, so the next step will be to figure out which antibodies are responsible for this, and how they promote fetal damage. This has significant implications for vaccine development; a safe Zika vaccine would have to selectively elicit antibodies that are protective, while avoiding those that potentially enhance the risk of microcephaly."

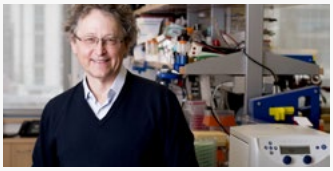


Anti-Zika antibodies from mothers whose children developed microcephaly (red) enhance the infectious activity of luciferase-labeled Zika reporter viruses more strongly than antibodies from mothers whose children developed normally (black).
Credit: Robbiani et al., 2019

RESEARCHER DETAILS

Davide F. Robbiani
Research Associate Professor; The Rockefeller University; drobbiani@rockefeller.edu

Photos courtesy of The Rockefeller University



Michel C. Nussenzweig
Zanvil A. Cohn and Ralph M. Steinman Professor; The Rockefeller University; Investigator, Howard Hughes Medical Institute; nussen@rockefeller.edu

ORIGINAL PAPER

Robbiani, D.F., P.C. Olsen, F. Costa, Q. Wang, T.Y. Oliveira, N. Nery, A. Aromolaran, M.S. do Rosário, G.A. Sacramento, J.S. Cruz, R. Khouri, E.A. Wunder, A. Mattos, B. de Paula Freitas, M. Sarno, G. Archanjo, D. Daltro, G.B.S. Carvalho, K. Pimentel, I.C. de Siqueira, J.R.M. de Almeida, D.F. Henriques, J.A. Lima, P.F.C. Vasconcelos, D. Schaefer-Babajew, S.A. Azzopardi, L. Bozzacco, A. Gazumyan, R. Belfort, A.P. Alcântara, G. Carvalho, L. Moreira, K. Araujo, M.G. Reis, R.I. Keesler, L.L. Coffey, J. Tisoncik-Go, M. Gale, L. Rajagopal, K.M. Adams Waldorf, D.M. Dudley, H.A. Simmons, A. Mejia, D.H. O'Connor, R.J. Steinbach, N. Haese, J. Smith, A. Lewis, L. Colgin, V. Roberts, A. Frias, M. Kelleher, A. Hirsch, D.N. Streblow, C.M. Rice, M.R. MacDonald, A.R.P. de Almeida, K.K.A. Van Rompay, A.I. Ko, and M.C. Nussenzweig. 2019. Risk of Zika microcephaly correlates with features of maternal antibodies. *J. Exp. Med.* 216:2302–2315.
https://doi.org/10.1084/jem.20191061

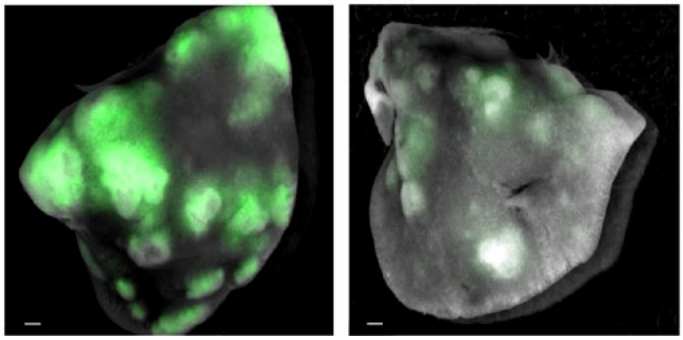
FERROPTOSIS DRIVES TUBERCULOSIS PATHOLOGY

Study finds that iron-induced cell death promotes tissue necrosis and facilitates mycobacterial spread

The World Health Organization estimates that tuberculosis killed 1.5 million people worldwide in 2018, the highest death toll for any disease caused by a single infectious agent. New approaches to treating the disease could involve targeting the host cell pathways triggered by *Mycobacterium tuberculosis* (Mtb) infection. For example, macrophages infected with Mtb can undergo necrosis, a proinflammatory form of cell death that contributes to tissue damage and may facilitate bacterial spread by releasing Mtb into the surrounding tissue.

There are, however, several different modes of necrosis with their own distinct triggers and effector molecules, and the precise pathways induced by Mtb infection have remained unclear. One recently discovered necrotic pathway is ferroptosis, in which elevated iron levels induce the production of hydrogen peroxides that react with membrane lipids to form toxic lipid peroxides capable of disrupting the plasma membrane. "Since iron overload is also known to promote tuberculosis under certain conditions, we wondered whether ferroptosis plays a role in the necrotic cell death and tissue necrosis triggered by Mtb infection," explains Alan Sher, a researcher at the National Institute of Allergy and Infectious Diseases.

Sher and colleagues, including first author Eduardo Amaral, examined mouse macrophages infected with Mtb and found that their necrotic death was accompanied by increases in intracellular iron and mitochondrial superoxide levels, as well as lipid peroxidation. Moreover, Mtb infection suppressed the expression of Gpx4, an enzyme that can reduce lipid peroxides and limit their toxic effects on the cell.

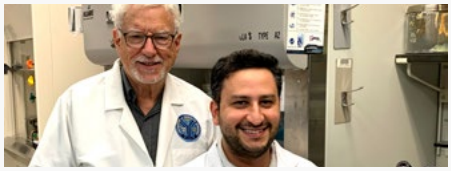


Sytox Green staining of lung tissue from Mtb-infected mice shows that, compared with a vehicle-treated control (left), tissue necrosis is reduced upon treatment with the ferroptosis inhibitor ferrostatin-1 (right).
Credit: Amaral et al., 2019

"The Mtb-induced death of macrophages in vitro therefore exhibits the major hallmarks of ferroptosis," Amaral says. Accordingly, treating these cells with an iron chelator or a ferroptosis inhibitor called ferrostatin-1 prevented their death upon Mtb infection.

Amaral et al. saw similar effects in vivo. Mice infected with Mtb showed a decrease in macrophage Gpx4 expression and an increase in lipid peroxide levels. Treatment with ferrostatin-1 suppressed pulmonary necrosis in these animals and reduced bacterial numbers in both the lungs and spleens, strongly suggesting that ferroptosis is critical to the spread of Mtb. "Clearly, further preclinical studies are required to validate ferroptosis as a viable target for host-directed therapy of active tuberculosis," Sher says. "But the potential to simultaneously lessen tissue damage while reducing pathogen burden and dissemination is an attractive aspect of this strategy."

RESEARCHER DETAILS



Alan Sher
Deputy Chief, Laboratory of Parasitic Diseases; Chief, Immunobiology Section; National Institute of Allergy and Infectious Diseases, National Institutes of Health; asher@nih.gov

Eduardo P. Amaral
Visiting Fellow; National Institute of Allergy and Infectious Diseases; National Institutes of Health; eduardo.amaral@nih.gov

ORIGINAL PAPER

Amaral, E.P., D.L. Costa, S. Namasivayam, N. Riteau, O. Kamenyeva, L. Mittereder, K.D. Mayer-Barber, B.B. Andrade, and A. Sher. 2019. A major role for ferroptosis in *Mycobacterium tuberculosis*–induced cell death and tissue necrosis. *J. Exp. Med.* 216:556–570.
https://doi.org/10.1084/jem.20181776

SECRETED SPLICE VARIANTS MEDIATE RESISTANCE TO ANTI-PD-L1 THERAPY

Non-small cell lung cancers can acquire resistance to immunotherapy by producing soluble versions of PD-L1 that can act as decoys and prevent immune checkpoint blockade

Many tumor cells evade the immune system by expressing high levels of the transmembrane protein PD-L1, which binds to its receptor, PD-1, on the surface of cytotoxic T cells and activates an immune checkpoint that inhibits T cell function. Therapeutic antibodies that prevent this checkpoint by binding to PD-1 or PD-L1 have proven to be beneficial treatments for a variety of cancers, from melanoma to non-small cell lung cancer (NSCLC).

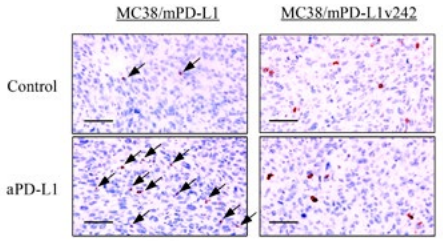
"However, the incidence of acquired resistance to PD-1 and PD-L1 blocking antibodies is increasing," says Ryohei Katayama from the Japanese Foundation for Cancer Research in Tokyo. "Several groups have described mechanisms underlying resistance to PD-1 blockade, but the mechanisms surrounding resistance to anti-PD-L1 treatment remain poorly understood."

Katayama's team, including first author Bo Gong, analyzed two NSCLC patients who initially responded to anti-PD-L1 treatment before undergoing a relapse and found that their relapsed tumors expressed splice variants of PD-L1 that lacked the protein's transmembrane domain. These splice variants are therefore secreted from cells, leading to high levels of soluble PD-L1 in the patients' blood and lung fluid. The same variants were also found in another 2 of 15 cancer patients who had acquired resistance to anti-PD-L1 therapy.

"We hypothesized that the secreted variants act as decoys that attenuate the neutralizing activity of anti-PD-L1 antibodies," says Gong. Indeed, the researchers found that soluble PD-L1 was able to compete for anti-PD-L1 antibodies, preventing them from binding to cell surface PD-L1 and reactivating T cells in vitro.

To test the effects of soluble PD-L1 in vivo, Katayama and colleagues injected mice with murine cancer cells expressing a secreted PD-L1 splice variant and found that the tumors formed by these cells were more resistant to anti-PD-L1 therapy. In fact, the researchers found, only 1% of cells need to express soluble PD-L1 for the tumor to be resistant to PD-L1 blockade. However, the tumors remained susceptible to anti-PD-1 antibodies, suggesting that these could be used as an alternative treatment for patients resistant to anti-PD-L1 therapy.

"Taken together, our findings suggest that the presence of soluble PD-L1 splicing variants or the level of soluble PD-L1 in plasma or pleural effusion may work as a biomarker to predict a patient's response to PD-L1 blockade therapy and that anti PD-1 antibody treatment could be a therapeutic option to overcome soluble PD-L1 variant–induced resistance," Katayama says.



Immune checkpoint blockade with anti-PD-L1 antibodies (bottom row) causes cytotoxic T cells expressing granzyme B (arrows) to accumulate in tumors overexpressing full-length membrane-bound PD-L1 (left). But tumors overexpressing soluble PD-L1 are resistant to anti-PD-L1 treatment (right).
Credit: Gong et al., 2019

RESEARCHER DETAILS

Ryohei Katayama
Chief, Division of Experimental Chemotherapy; Cancer Chemotherapy Center; Japanese Foundation for Cancer Research;
ryohei.katayama@jfcr.or.jp

Bo Gong
Postdoctoral researcher; Division of Experimental Chemotherapy; Cancer Chemotherapy Center; Japanese Foundation for Cancer Research

ORIGINAL PAPER

Gong, B., K. Kiyotani, S. Sakata, S. Nagano, S. Kumehara, S. Baba, B. Besse, N. Yanagitani, L. Friboulet, M. Nishio, K. Takeuchi, H. Kawamoto, N. Fujita, and R. Katayama. 2019. Secreted PD-L1 variants mediate resistance to PD-L1 blockade therapy in non–small cell lung cancer. *J. Exp. Med.* 216:982–1000.
https://doi.org/10.1084/jem.20180870

HETEROTYPIC SPHEROIDS DRIVE OVARIAN CANCER METASTASIS

Fibroblasts and ascitic cancer cells form metastatic units that promote the dissemination of tumor cells throughout the abdominal cavity

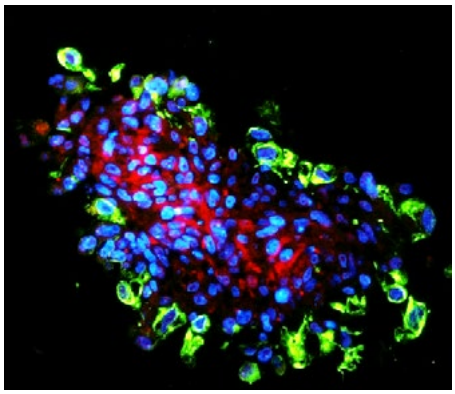
High-grade serous ovarian cancer (HGSOC)—the most aggressive form of ovarian cancer—is characterized by the early and rapid dissemination of cancer cells to other sites within the abdomen. Cancer cells that escape from the primary tumor are thought to form spheroids in the ascitic fluid that accumulates in HGSOC patients. These spheroids can then attach to the peritoneal membrane that lines the abdominal cavity and invade the underlying extracellular matrix to form secondary, metastatic tumors.

"Given the proposed function of spheroids during ovarian cancer metastasis, we wanted to investigate the processes by which ascitic tumor cells (ATCs) assemble into spheroids and execute peritoneal dissemination," says Qinglei Gao from Tongji Medical College, Huazhong University of Science and Technology in Wuhan, China.

Gao and colleagues, including co-first author Zongyuan Yang, found that ATCs from HGSOC patients tend to form heterotypic spheroids with cancer-associated fibroblasts (CAFs) present in the ascites. These CAFs protect the cancer cells from apoptosis and facilitate their invasion of the peritoneum, eventually forming the stroma of the newly formed metastases. "Due to their inherent malignant potential and contribution to peritoneal dissemination, we termed these CAF-containing heterospheroid structures metastatic units," Gao says. "Intriguingly, stromal fibroblasts and the resultant heterospheroids are rarely found in low-grade serous ovarian cancer, which might explain its reduced tendency for dissemination."

Gao's team determined that ATCs from HGSOC patients express high amounts of integrin α5, a cell adhesion molecule whose levels correlate with poor patient outcomes. The researchers found that integrin α5 mediates the association of ATCs with fibroblasts during spheroid formation and that EGF secreted from these fibroblasts subsequently helps to sustain integrin α5 expression. Inhibiting this signaling pathway with a neutralizing anti-EGF antibody impaired spheroid formation and reduced peritoneal tumor burden in mice injected with both ATCs and CAFs.

Gao et al.'s results suggest that targeting CAFs could prevent metastasis in HGSOC patients. The researchers found that early administration of imatinib, a tyrosine kinase inhibitor that can eliminate CAFs by blocking PDGF signaling, reduced tumor burden and improved survival in a mouse model of metastatic ovarian cancer. This treatment was even more effective when combined with liposome clodronate to additionally eliminate tumor-associated macrophages, which have also been reported to promote spheroid formation in ovarian cancer.



Heterotypic spheroids consisting of epithelial cancer cells (green) surrounding a core of fibroblasts (red) form in the ascites of HGSOC patients. These spheroids act as metastatic units that facilitate the dissemination of ovarian cancer cells throughout the abdominal cavity.
Credit: Gao et al., 2019

"Together, our results suggest that early targeting of stromal CAFs to destroy metastatic units could be a new therapeutic strategy to limit HGSOC progression," Gao says.

RESEARCHER DETAILS

Qinglei Gao
Professor; Tongji Medical College; Huazhong University of Science and Technology;
qingleigao@hotmail.com

Zongyuan Yang
Attending doctor, Assistant research fellow; Tongji Medical College; Huazhong University of Science and Technology

ORIGINAL PAPER

Gao, Q., Z. Yang, S. Xu, X. Li, X. Yang, P. Jin, Y. Liu, X. Zhou, T. Zhang, C. Gong, X. Wei, D. Liu, C. Sun, G. Chen, J. Hu, L. Meng, J. Zhou, K. Sawada, R. Fruscio, T.W. Grunt, J. Wischhusen, V.M. Vargas-Hernández, B. Pothuri, and R.L. Coleman. 2019. Heterotypic CAF-tumor spheroids promote early peritoneal metastasis of ovarian cancer. *J. Exp. Med.* 216: 688–703.
https://doi.org/10.1084/jem.20180765

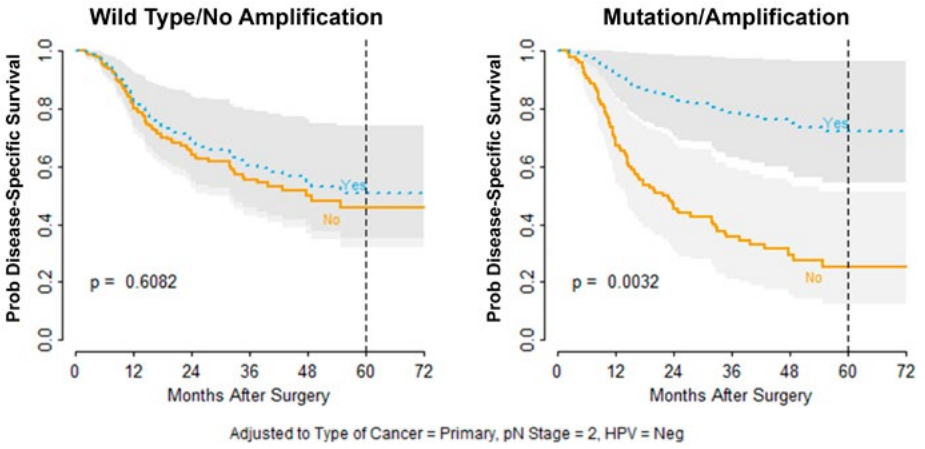
ASPIRIN MAY HELP SOME PATIENTS SURVIVE HEAD AND NECK CANCER

By lowering prostaglandin E_2 levels, regular use of aspirin or other NSAIDs could prolong the life of patients with mutations in the *PIK3CA* gene

Head and neck squamous cell carcinoma (HNSCC) accounts for about 4% of all cancers in the United States and continues to have high rates of patient mortality. Risk factors for HNSCC include smoking, alcohol use, and human papillomavirus infection, but several studies have shown that regular use of aspirin can reduce the risk of developing the disease. However, whether aspirin or other nonsteroidal anti-inflammatory drugs (NSAIDs) can promote the survival of patients who have already developed HNSCC is unclear; studies investigating this question have so far produced conflicting results.

One possibility is that NSAIDs are only effective against some types of HNSCC. Around 35% of HNSCC tumors carry mutations that activate the *PIK3CA* gene, which encodes the catalytic subunit of the signaling enzyme PI3Kα. Researchers led by Professor Jennifer Grandis at the University of California, San Francisco, investigated whether regular NSAID use specifically improved the survival of HNSCC patients with alterations in the *PIK3CA* gene.

The researchers analyzed a group of 266 HNSCC patients who had had their tumors surgically removed and, in most cases, were then treated with adjuvant chemotherapy and/or radiotherapy. Patients without any alterations in their *PIK3CA* gene were no better off if they also took NSAIDs on a regular basis (defined as two or more doses per week for at least six months). By contrast, regular NSAID usage dramatically enhanced the survival of patients whose *PIK3CA* gene was mutated and/or amplified. Among these patients, NSAIDs increased the overall five-year survival rate from 25% to 78%.



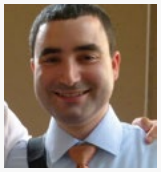
Compared with no or occasional NSAID usage (orange lines), regular NSAID use (blue lines) had no effect on the survival of HNSCC patients with wild-type *PIK3CA* (left), but dramatically increased the survival of patients with a mutated or amplified *PIK3CA* gene (right).
Credit: Hedberg et al., 2019

NSAIDs also inhibited tumor growth in mice injected with cancer cells harboring a mutant *PIK3CA* gene. By analyzing these mice, Grandis and colleagues found that NSAIDs likely inhibit tumor growth by reducing the production of prostaglandin E_2. This proinflammatory molecule has been implicated in a variety of cancers and can be induced by the PI3Kα signaling pathway. NSAIDs may therefore also be effective against a variety of cancers that contain activating mutations in *PIK3CA*. Indeed, previous studies have shown that regular aspirin usage can aid the survival of colorectal cancer patients carrying mutated *PIK3CA*.

"The present study is the first to demonstrate that regular NSAID usage confers a significant clinical advantage in patients with *PIK3CA*-altered HNSCC," Grandis says. "Inconsistencies in the type, timing, and dosages of NSAIDs taken by patients in this study limit our ability to make specific therapeutic recommendations. But the magnitude of the apparent advantage, especially given the marked morbidity and mortality of this disease, warrants further study in a prospective, randomized clinical trial."

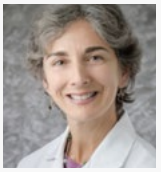
RESEARCHER DETAILS

Matthew L. Hedberg
MD-PhD student; University of Pittsburgh School of Medicine



Noah D. Peyser
Project manager; University of California, San Francisco

Julie E. Bauman
Professor of Medicine; University of Arizona



Jennifer R. Grandis
American Cancer Society Professor; University of California, San Francisco
jennifer.grandis@ucsf.edu

ORIGINAL PAPER

Hedberg, M.L., N.D. Peyser, J.E. Bauman, W.E. Gooding, H. Li, N.E. Bhola, T.R. Zhu, Y. Zeng, T.M. Brand, M.-O. Kim, R.C.K. Jordan, S. VandenBerg, V. Olivas, T.G. Bivona, S.I. Chiosea, L. Wang, G.B. Mills, J.T. Johnson, U. Duvvuri, R.L. Ferris, P. Ha, D.E. Johnson, and J.R. Grandis. 2019. Use of nonsteroidal anti-inflammatory drugs predicts improved patient survival for *PIK3CA*-altered head and neck cancer. *J. Exp. Med.* 216:419-427.
https://doi.org/10.1084/jem.20181936

ANTIBIOTIC TREATMENT ALLEVIATES ALZHEIMER'S DISEASE SYMPTOMS IN MALE MICE

By altering the gut microbiome, long-term antibiotic treatment reduces inflammation and slows the growth of amyloid plaques in male APPPS1-21 mice

The community of bacteria that live in the gastrointestinal tract—the gut microbiome—is generally harmless, but, because they affect the activity of the body's immune system, these bacteria can influence a wide range of diseases, even in distant tissues such as the brain.

"Recent evidence suggests that intestinal bacteria could play a major role in various neurological conditions including autism spectrum disorders, multiple sclerosis, Parkinson's disease, and Alzheimer's disease (AD)," explains Sangram Sisodia from The University of Chicago.

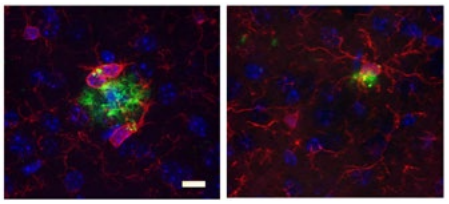
AD is characterized by the formation of amyloid plaques and the activation of brain-resident immune cells called microglia. These cells can help remove amyloid plaques, but their activation may also exacerbate the disease by causing neuroinflammation.

AD patients exhibit changes in their gut microbiome, and Sisodia and colleagues previously found that gut bacteria may influence the development of Alzheimer's-like symptoms in rodents. Long-term antibiotic treatment limited the formation of amyloid plaques and reduced microglia activation in male, but not female, $APP_{SWE}/PS1_{\Delta E9}$ mice, which express mutant proteins associated with familial AD. "While compelling, our published studies on the role of the gut microbiome on amyloid plaque formation were limited to a single strain of mice," Sisodia says.

Sisodia and colleagues, including first author Hemraj Dodiya, therefore examined the effects of antibiotics on a different mouse model of AD known as APPPS1-21. Long-term treatment with a cocktail of antibiotics again reduced the formation of amyloid plaques in male mice but had no effect on females. Antibiotic treatment also appeared to alter the activation of microglia in male mice, changing them from a form that is thought to promote neurodegeneration to a form that helps to maintain a healthy brain.

To prove that these improvements in Alzheimer's symptoms were caused by alterations in the gut microbiome, the researchers transplanted fecal matter from untreated mice into antibiotic-treated animals. This procedure restored the gut microbiome and caused an increase in amyloid plaque formation and microglial activation.

But why do alterations in the gut microbiome only affect male mice? Sisodia and colleagues discovered that long-term antibiotic treatment changed the gut bacteria of male and female mice in different ways. The changes in the microbiome of female mice caused their immune systems to increase production of several proinflammatory factors that could influence the activation of microglia.



Compared with a control (left), long-term antibiotic treatment (right) reduces the size of amyloid plaques (green) and alters the appearance of microglia (red) in the brains of male APPPS1-21 mice.
Credit: Dodiya et al., 2019

"Our study shows that antibiotic-mediated perturbations of the gut microbiome have selective, sex-specific influences on amyloid plaque formation and microglial activity in the brain," Sisodia says. "We now want to investigate whether these outcomes can be attributed to changes in any particular type of bacteria."

RESEARCHER DETAILS

Hemraj B. Dodiya
Postdoctoral scholar; The University of Chicago

Sangram S. Sisodia
Thomas Reynolds Sr. Family Professor of Neurosciences; Director, Center for Molecular Neurobiology; The University of Chicago
ssisodia@bsd.uchicago.edu

ORIGINAL PAPER

Dodiya, H.B., T. Kuntz, S.M. Shaik, C. Baufeld, J. Leibowitz, X. Zhang, N. Gottel, X. Zhang, O. Butovsky, J.A. Gilbert, and S.S. Sisodia. 2019. Sex-specific effects of microbiome perturbations on cerebral Aβ amyloidosis and microglia phenotypes. *J. Exp. Med.* 216:1542–1560.
https://doi.org/10.1084/jem.20182386

STROKE DRUG MAY ALSO PREVENT ALZHEIMER'S DISEASE

The genetically engineered protein 3K3A-APC reduces amyloid-β deposition in mice by inhibiting transcription of BACE1

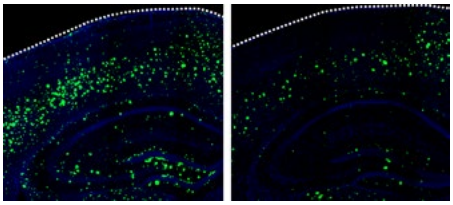
3K3A-APC is a genetically modified version of a human blood protein called activated protein C, which reduces inflammation and protects both neurons and the cells that line the walls of blood vessels from death and degeneration. 3K3A-APC has beneficial effects in various mouse models of disease, including traumatic brain injury and multiple sclerosis, and is currently being developed to treat stroke in humans, where it has been shown to be safe, well tolerated, and capable of reducing intracerebral bleeding.

"Because of its neuroprotective, vasculoprotective, and anti-inflammatory activities in multiple models of neurological disorders, we investigated whether 3K3A-APC can also protect the brain from the toxic effects of amyloid-β toxin in a mouse model of Alzheimer's disease," says Berislav V. Zlokovic, Director of the Zilkha Neurogenetic Institute at the Keck School of Medicine, University of Southern California.

Toxic amyloid-β peptides accumulate in the brains of Alzheimer's patients, leading to neurodegeneration and reduced blood flow within the brain. Zlokovic and colleagues, including co-first authors Divna Lazic and Abhay Sagare, found that a four-month course of daily 3K3A-APC injections significantly reduced amyloid-β deposition in the brains of 5XFAD mice, which usually produce large amounts of the toxic peptide. 3K3A-APC treatment prevented these mice from losing their memory and helped maintain normal cerebral blood flow. By reducing the levels of microglia and proinflammatory cytokines, 3K3A-APC also suppressed inflammation within the brain, another common feature of Alzheimer's disease.

Zlokovic and colleagues found that 3K3A-APC protects the brain by inhibiting the NF-κB-dependent transcription of BACE1, a protease that helps generate amyloid-β by cleaving amyloid precursor protein. 3K3A-APC inhibited the activation of NF-κB in neurons, resulting in a 50% reduction of BACE1 levels in the cortex.

Several different inhibitors of BACE1 have been tested in clinical trials for Alzheimer's disease, but the new study suggests that using 3K3A-APC to block the expression of BACE1 could be an alternative approach, particularly at early stages of the disease, when amyloid-β has yet to accumulate to levels capable of permanently damaging the brain. Besides suppressing inflammation independently of its anti-amyloidogenic effect, 3K3A-APC also directly protects neurons and brain vasculature from the toxic effects of amyloid-β.



Compared with a control (left), 3K3A-APC treatment (right) greatly reduces the accumulation of amyloid-β (green) in the brains of 5XFAD mice. Credit: Lazic et al., 2019

"Our present data support the idea that 3K3A-APC holds potential as an effective anti–amyloid-β therapy for early stage Alzheimer's disease in humans," Zlokovic says.

RESEARCHER DETAILS

Divna Lazic
Research Scholar; Zilkha Neurogenetic Institute; Keck School of Medicine; University of Southern California

Abhay P. Sagare
Assistant Professor; Zilkha Neurogenetic Institute; Keck School of Medicine; University of Southern California

Berislav V. Zlokovic
Director; Zilkha Neurogenetic Institute; Keck School of Medicine; University of Southern California;
zlokovic@usc.edu

ORIGINAL PAPER

Lazic, D., A.P. Sagare, A.M. Nikolakopoulou, J.H. Griffin, R. Vassar, and B.V. Zlokovic. 2019. 3K3A-activated protein C blocks amyloidogenic BACE1 pathway and improves functional outcome in mice. *J. Exp. Med.* 216:279–293.
https://doi.org/10.1084/jem.20181035

THANK YOU TO OUR REVIEWERS

We are grateful to the following researchers who contributed their time and expertise to ensure the publication of quality science at *JEM* in 2019. *JEM* is committed to recognizing the service of our reviewers and is pleased to partner with Publons and ORCID as platforms to document their contributions.

Omar Abdel-Wahab
Laurent Abel
Andrea Ablasser
Marc Achen
Iannis Adamopoulos
Erin Adams
Ralf Adams
Adam Adler
Prasad Adusumilli
William Agace
Dritan Agalliu
Rafi Ahmed
Iannis Aifantis
Alessandro Aiuti
Bahareh Ajami
Katerina Akassoglou
Shizuo Akira
Balbino Alarcon
Pilar Alcaide
Jessy Alexander
Andrea Alimonti
Kari Alitalo
Todd Allen
Abdullah Alli
David Allman
Frederick Alt
Brian Altman
Graham Anderson
Kellie Ann Jurado
Josef Anrather
K. Mark Ansel
Rajendra Apte
Scott Armstrong
David Artis
Maxim Artyomov
Avery August
Dorina Avram
Frances Balkwill
Jacques Banchereau
Oliver Bannard
Shideng Bao
Nick Barker
Dan Barouch
Franck Barrat
Alan D.T. Barrett
Armando Bartolazzi
Dirk Baumjohann
Isabel Beerman
Jürgen Behrens
Gabrielle Belz
Yinon Ben-Neriah
Albert Bendelac
Salvador Benitah
Jeffrey Benovic
Cornelia Bergmann
Irwin Bernstein
Antonio Bertoletti
Stuart Berzins
Semir Beyaz
Vivien Beziat
Avinash Bhandoola
Nina Bhardwaj
Deepta Bhattacharya
Christine Biron
Subhra Biswas
Joshua Black
Victoria Blaho
Catherine Blish
Jeffrey Bluestone
Richard Blumberg
Mathew Blurton-Jones
Justin Boddey
Manfred Boehm
Christian Bogdan
Bertrand Boisson
Sebastien Bonnet
Karin Bornfeldt
Vassiliki Boussiotis
Joshua Boyce
Marjorie Brand
Jason Brenchley
Emery Bresnick
Thomas Brocker
Petter Brodin
Igor Brodsky
Vincenzo Bronte
David Brooks
Hal Broxmeyer
Clare Bryant
Yenan Bryceson
Guojun Bu
Juliane Bubeck Wardenburg
Rebecca Buckley
Jane Buckner
G.R. Budinger
Sven Burgdorf
Dennis Burton
Meinrad Busslinger
Eugene Butcher
Jason Butler
Noah Butler
Oleg Butovsky
Tatiana Byzova
Jorge Caamano
Nina Cabezas-Wallscheid
Ken Cadwell
George Calin
Daniel Campbell
Michael Cancro
Qi Cao
Yihai Cao
Roxana Carare
Francis Carbone
Nadia Carlesso
S. Thomas Carmichael
Pico Caroni
Arturo Casadevall
Paolo Casali
Toni Celià-Terrassa
Craig Ceol
Andrea Cerutti
Adelheid Cerwenka
Grant Challen
Jonah Chan
Jayanta Chaudhuri
Dong Feng Chen
Huanhuan Chen
Jichao Chen
Wanjun Chen
Yu Chen
Jonathan Chernoff
Sara Cherry
Milan Chheda
Hongbo Chi
Yueh-hsiu Chien
Augustine Choi
Christine Choi
Jae-Hoon Choi
Amy Chung
John Chute
Daniela Čiháková
Elisabetta Citterio
Björn Clausen
Hans Clevers
Michel Cogné
Paul Cohen
Lillian Cohn
Marco Colonna
Yingzi Cong
Marcus Conrad
Gabriela Constantin
Matthew Cook
Angel Corbí
Eva Corey
Valerie Cormier-Daire
Kevin Couper
Joseph Craft
Howard Crawford
John Crispino
Ben Croker
Shane Crotty
Ronald Crystal
Weiguo Cui
Myron Cybulsky
Jason Cyster
Laura Danai
Anne Davidson
Gerald De Haan
Ruggero De Maria
Karin De Visser
Jolanda De Vries
Rene De Waal Malefyt
Rashid Deane
Thomas Decker
Anthony DeFranco
Giannino Del Sal
Greg Delgoffe
Ruud Delwel
Gina DeNicola
Mieke Dewerchin
Javier Di Noia
James Di Santo
Michael Diamond
Sven Diederichs
Andreas Diefenbach
Stanislav Dikiy
Stefanie Dimmeler
Donato DiMonte
Lei Ding
Lei Ding
David Dominguez-Sola
Chen Dong

Stephanie Dougan
Glenn Dranoff
Anette Duensing
Darragh Duffy
Elaine Dzierzak
Gerard Eberl
Matthias Eberl
Mikala Egeblad
Lauren Ehrlich
Anne Eichmann
Stephanie Eisenbarth
Joseph El Khoury
Britta Engelhardt
Neta Erez
Justin Eyquem
Elena Ezhkova
Sidonia Fagarasan
Donna Farber
Henner Farin
Michael Farrar
James Fawcett
Yongqiang Feng
Stefan Feske
Markus Feuerer
Anthony Filiano
Marie-Dominique Filippi
Katherine Fitzgerald
James Fox
Nikolaos Frangogiannis
Paul Frenette
Martin Friedlander
Scott Friedman
John Fryer
Mingui Fu
Yang-Xin Fu
Shin-ichiro Fujii
Dmitry Gabrilovich
Sarah Gaffen
Thomas Gajewski
Stephen Galli
Li Gan
Laurent Gapin
Adolfo Garcia-Sastre
Gaetano Gargiulo
Cecilia Garlanda
Nicholas Gascoigne
Georg Gasteiger
Luca Gattinoni
Jack Gauldie
Patricia Gearhart
Raif Geha
Teunis Geijtenbeek
Michael Gerner
Cyrus Ghajar
Susan Gilfillan
Derek Gilroy
Florent Ginhoux
Jean-Philippe Girard
Joseph Gleeson

Dale Godfrey
Todd Golde
Ananda Goldrath
Mary Goldring
Harris Goldstein
Douglas Golenbock
Christopher Goodnow
Helen Goodridge
Siamon Gordon
Stanislas Goriely
Joan Goverman
John Grainger
Joe Gray
Benjamin Greenbaum
Florian Greten
Tim Greten
Melanie Greter
H. Leighton Grimes
Sergei Grivennikov
Olaf Gross
Christoph Grundner
Greta Guarda
Johann Gudjonsson
Pierre Guermonprez
Nadia Guerra
Martin Guilliams
Christina Gurnett
David Hafler
Marcia Haigis
Tim Halim
Sophie Hambleton
Jessica Hamerman
Jiahuai Han
Douglas Hanahan
Gunnar Hansson
Laurie Harrington
Isaac Harris
David Harrison
Nissim Hay
Barton Haynes
Stephen Hedrick
Vigo Heissmeyer
Werner Held
Saskia Hemmers
Rudi Hendriks
Michael Heneka
Matthew Hepworth
DeBroski Herbert
Meenhard Herlyn
Betsy Herold
Daniel Herranz
Michael Hickey
Andrés Hidalgo
David Hildeman
Ann Hill
Claire Hivroz
Timothy Hla
Ping-Chih Ho
Ted Ho

Hal Hoffman
Kristin Hogquist
Steven Holland
Shohei Hori
Franck Housseau
Hongzhen Hu
Jian Hu
Xiaoyu Hu
Bo Huang
Gang Huang
Yadong Huang
David Hunstad
Robert Hunt
Christopher Hunter
Nicholas Huntington
Sun Hur
Morgan Huse
Richard Hynes
Matteo Iannacone
Juliana Idoyaga
Fumiyo Ikeda
Denise Inman
Luisa Iruela-Arispe
Ken Ishii
Ivaylo Ivanov
Kazuhiro Iwai
Yasuko Iwakiri
Atsushi Iwama
Akiko Iwasaki
Bana Jabri
Eileen Jaffe
Frode Jahnsen
Sébastien Jaillon
Rakesh Jain
Julie Jameson
Stephen Jameson
Bassam Janji
Dragana Jankovic
Tobias Janowitz
Lukas Jeker
Kim Jensen
You Jeong Lee
Susan John
Emmanuelle Jouanguy
Kenji Kabashima
Jonathan Kagan
Tsuneyasu Kaisho
Axel Kallies
Raghu Kalluri
Takashi Kanaya
Lawrence Kane
Joonsoo Kang
Yibin Kang
Thirumala-Devi Kanneganti
Daniel Kaplan
Mark Kaplan
Stefan Kappe
Florian Karreth
Gerard Karsenty

James Kavanagh
Taro Kawai
Nobuhiko Kayagaki
Ross Kedl
Barbara Kee
John Kehrl
Michelle Kelliher
Brian Kelsall
Bradley Kerr
Rajiv Khanna
Sundeep Khosla
Carla Kim
Juhyun Kim
Jungsu Kim
William Kim
Katherine King
Jonathan Kipnis
Florian Klein
Ludger Klein
Robyn Klein
Ulf Klein
Christoph Kleinschnitz
Paul Klenerman
Sarah Knox
George Kollias
Jay Kolls
Manfred Kopf
Thomas Korn
Richard Koup
Shigeo Koyasu
Florian Krammer
Kamil Kranc
Michael Krangel
Mitchell Kronenberg
Paul Kubes
Thomas Kupper
Ralf Kuppers
Tomohiro Kurosaki
Christian Kurts
David Kwiatkowski
Robert Lafyatis
Mohamed Lamkanfi
Philipp Lang
Olivier Lantz
Antonio Lanzavecchia
Sylvain Latour
Marc Lecuit
Chih-Hao Lee
Jongsoon Lee
Michael Lenardo
Claudia Lengerke
David Levens
Megan Levings
David Levy
Klaus Ley
Steven Ley
Linheng Li
Ming Li
Qing Li

Wei Li
Xiao-Jiang Li
Xiaoxia Li
Yueming Li
Zhang Li
Peter Libby
Judy Lieberman
Egil Lien
Arthur Liesz
Foo Liew
Brett Lindenbach
Michelle Linterman
Adrian Liston
Feng Liu
Huiping Liu
Karen Liu
Yingjun Liu
Yun-Cai Liu
Richard Locksley
Bart Loeys
Gregory Longmore
Michael Lotze
Clifford Lowell
Paul Lu
Theresa Lu
Zhimin Lu
Carrie Lucas
Daniel Lucas
Burkhard Ludewig
Enrico Lugli
Amaia Lujambio
Eline Luning Prak
Francis Luscinskas
Andrew Luster
Sanjiv Luther
Nils Lycke
David Lyden
David Lyons
Averil Ma
Jian-xing Ma
Xiaojing Ma
Neil Mabbott
Margaret MacDonald
Halina Machelska
Laura Mackay
Elizabeth Maher
Rick Maizels
Ravindra Majeti
Tak Mak
Thomas Malek
Asrar Malik
Bernard Malissen
Ziad Mallat
Giovanna Mallucci
Karl-Johan Malmberg
Maksim Mamonkin
Nicolas Manel
John Manis
Amity Manning

Alberto Mantovani
Daniel Marks
Eric Marsh
Inga-Lill Mårtensson
Seamus Martin
David Masopust
Joan Massague
Diane Mathis
Mehrdad Matloubian
Tanya Mayadas
Jared Mayers
Massimiliano Mazzone
Joseph R. Mazzulli
Florencia McAllister
Maureen McGargill
Dorian McGavern
Mandy McGeachy
Andrew McGuire
Andrew McMichael
Eric Meffre
Wajahat Mehal
Joseph Melenhorst
Ignacio Melero
Simón Méndez-Ferrer
George Mentiz
Christian Metallo
Isabelle Meyts
George Miller
Robert Miller
Timothy Miller
Simon Milling
Thomas Milne
Joshua Milner
Jonathan Miner
Veronique Miron
Tom Misteli
Michael J. Mitchell
Jenny Mjösberg
Edward Mocarski
Ari Molofsky
Michelle Monje
Tony Moody
Tomohiro Morio
Craig Morrell
Eric Morrow
Jennifer Morton
Muriel Moser
David Mosser
Maria Mota
Allan Mowat
Daniel Mucida
Scott Mueller
Debabrata Mukhopadhyay
Charles Mullighan
Mary Munson
Christian Munz
Kenneth Murphy
Peter Murray
Cornelis Murre

Ruth Muschel
Markus Müschen
Laszlo Nagy
Matthias Nahrendorf
Toshinori Nakayama
William Nauseef
David Nemazee
Kim Newton
Lai Guan Ng
Bernhard Nieswandt
David Nikolic-Paterson
Ralph Nixon
Luigi Notarangelo
John O'Shea
Tim O'Sullivan
Daniel Öhlund
Naoko Ohtani
Satoshi Okada
Klaus Okkenhaug
Afam Okoye
Daniel Olive
Eugene Oltz
Joost Oppenheim
Jordan Orange
Robert Orchard
Moishe Oren
Elisa Oricchio
Wenjun Ouyang
Huib Ovaa
Oliver Pabst
Timothy Padera
Christopher Paige
Peter Palese
Noah Palm
Karolina Palucka
Søren Paludan
Fan Pan
Katherine Panageas
Giuseppe Pantaleo
Jack Parent
Christopher Park
Jung-Hyun Park
Chandrashekhar Pasare
Virginia Pascual
Laura Pasqualucci
Tanya Paull
Erika L Pearce
R. Stokes Peebles
Roberta Pelanda
Sandra Pellegrini
Joao Pereira
Justin Perry
Rachel Perry
Karlheinz Peter
Tatiana V Petrova
Tri Phan
Laura Piccio
Stefano Piccolo
Alicia Pickrell

Eric Pietras
Smitha Pillai
Hidde Ploegh
Edward Plow
Amanda Poholek
Jeffrey Pollard
Richard Possemato
Murali Prakriya
Clare Pridans
Alice Prince
Marco Prinz
Anne Puel
Bali Pulendran
Ellen Pure
Yuliya Pylayeva-Gupta
Hai Qi
Daniela Quail
Sergio Quezada
Francisco Quintana
Cristina Rada
Freddy Radtke
Klaus Rajewsky
Ricardo Rajsbaum
Troy Randall
Gwendalyn Randolph
Rino Rappuoli
Vijay Rathinam
Michael Rauchman
David Raulet
Steven Reed
Jan Rehwinkel
Hans-Christian Reinecker
Boris Reizis
Nicholas Restifo
Bruno Reversade
Teresa Reyes
Claude-Agnes Reynaud
Antoni Ribas
Jeremy Rich
Alan Rickinson
James Riley
Mercedes Rincon
John Rinn
Robert Rissman
Amariliz Rivera
Davide Robbiani
Inez Rogatsky
Chiara Romagnani
Luigina Romani
Ru Rong Ji
Stefan Rose-John
Oren Rosenberg
Michael Rosenblum
Philip Rosenstiel
Karl Rudolph
David Ruggero
Anil Rustgi
Daniel Saban
Michel Sadelain

Supriya Saha
Federica Sallusto
Michael Samuel
Vanessa Sancho-Shimizu
David Sancho
Stefano Santaguida
Toshiro Sato
Ansuman Satpathy
Peter Savage
Ram Savan
Paul Sawchenko
Paola Scaffidi
Dorothy Schafer
Alexander Scheffold
Philipp Scherer
Andreas Schlitzer
Marc Schmidt-Supprian
Nathalie Schmitt
Kate Schroder
Susan Schwab
Robert Schwabe
Markus Schwaninger
Michal Schwartz
Olivier Schwartz
Pamela Schwartzberg
Benjamin Segal
Cyril Seillet
Rafick-Pierre Sekaly
Jyoti Sen
Carlos Serezani
Virginia Shapiro
Dmitry Shayakhmetov
Samuel Shelburne
Alan Sher
Brian Sheridan
Ethan Shevach
Pei-Yong Shi
Yongsheng Shi
Sunny Shin
Ramesh Shivdasani
Ziv Shulman
Eric Shusta
L. Sibley
Antonio Sica
Robert Siliciano
John Silke
Roy Silverstein
Guido Silvestri
Alfred Singer
Harinder Singh
Mihaela Skobe
Radek Skoda
Mark Slifka
Kenneth Smith
Ryan Smith
Hans-Willem Snoeck
Andrew Snow
Mark Snyder
Ole Søgaard
Gregory Sonnenberg
Lydia Sorokin
Janet Sparrow
Nancy Speck
Anne Sperling
Hergen Spits
Jonathan Sprent
Steven Stacker
Peter Staeheli
Christina Stallings
Leonidas Stamatatos
E. Richard Stanley
Ulrich Steidl
Christoph Stein
Jens Stein
Lawrence Steinman
Daniel Stetson
Brigitta Stockinger
Patrizia Stoitzner
Sean Stowell
Warren Strober
Helen Su
Lishan Su
David Sulzer
Jie Sun
Joseph Sun
Shao-Cong Sun
Eric Sundberg
Mark Sundrud
Fayyaz Sutterwala
Catharina Svanborg
Camilla Svensson
Filip Swirski
Nobuaki Takahashi
Osamu Takeuchi
Stuart Tangye
Ichiro Taniuchi
David Tarlinton
Marco Tartaglia
Steven Teitelbaum
Vinay Tergaonkar
Clotilde Thery
Paul Thomas
Ranjeny Thomas
Edward Thorp
Adrian Thrasher
Robert Tighe
Jenny Ting
Hervé Tiriac
Kai-Michael Toellner
Elena Tomasello
Ivan Topisirovic
María Toribio
Aminata Touré
Bruce Trapnell
Giorgio Trinchieri
Alexandra Trkola
Lloyd Trotman
Jennifer Trowbridge
Andreas Trumpp
Oleg Tsodikov
George Tsokos
Hidekazu Tsukamoto
Rubin Tuder
Shannon Turley
Martin Turner
Stephen Turner
Irina Udalova
Sophie Ugolini
Emil Unanue
Golnaz Vahedi
Jaap Van Buul
Jo Van Ginderachter
Luc Van Kaer
Rene Van Lier
Maarten Van Lohuizen
Russell Vance
Bart Vandekerckhove
Matthew Vander Heiden
Robert Vassar
Andrea Velardi
Amit Verma
David Vermijlen
Dietmar Vestweber
Gabriel Victora
Monika Vig
Ivan Vijovic-Cvjin
Carola Vinuesa
Eric Vivier
Matthias Von Herrath
Domagoj Vucic
Andreas Wack
Ari Waisman
Linda Wakim
Bruce Walker
Lary Walker
David Wallach
Thierry Walzer
Shizhen Wang
Sibao Wang
Kounosuke Watabe
David Watkins
Tania Watts
Alissa Weaver
Valerie Weaver
Robert Weinberg
Arthur Weiss
Mitchell Weiss
William Weiss
Hartmut Wekerle
Hans-Guido Wendel
Jason Whitmire
Linda Wicker
Heinz Wiendl
Christoph Wilhelm
Matthew Williams
Patrick Wilson
Douglas Winton
David Withers
Catherine Wu
Zhijian Wu
Kai Wucherpfennig
Thomas Wynn
Tony Wyss-Coray
Huaxi Xu
Masahiro Yamamoto
Kelley Yan
Nan Yan
Riqiang Yan
George Yap
Felix Yarovinsky
Jonathan Yewdell
Wayne Yokoyama
Benjamin Youngblood
Jianhua Yu
Laurent Yvan-Charvet
Alexander Zarbock
Hassane Zarour
Dietmar Zehn
Christina Zeitz
Santiago Zelenay
Rugang Zhang
Shen-Ying Zhang
Xiang Zhang
Hui Zheng
Lei Zheng
Ye Zheng
Binhua Zhou
Dawang Zhou
Jinfang Zhu
Julie Zikherman
Laurence Zitvogel
Berislav Zlokovic
Weiping Zou
Juan Carlos Zuniga-Pflucker

Rockefeller University Press

Journal of Experimental Medicine (ISSN 0022-1007) is published monthly by Rockefeller University Press, 950 Third Avenue, New York, NY 10022. Periodical postage paid at New York, NY and additional mailing offices.

2020 Subscription Rates
Institutional Rates

	Tier 1	Tier 2	Tier 3	Tier 4
Online	$1,780	$2,340	$3,170	$4,050
Print + Online	$3,990	$4,480	$5,030	$6,430

For more information, please contact our subscription office.
Phone: +1 860-350-0041
Fax: +1 860-350-0039
email: subs@rockefeller.org

Advertising Requests
Phone: 201-767-4170
email: rupads@rockefeller.edu

Permission Requests
email: permissions@rockefeller.edu

Media Requests
email: news@rockefeller.edu

Postmaster
Send address changes to *Journal of Experimental Medicine*, Subscription Office, The Bleachery, 143 West Street, New Milford, CT 06776.