JCI This Month

July 2017

A summary of the most recent articles in **The Journal of Clinical Investigation** and **JCI Insight**

ALSO IN THIS ISSUE:

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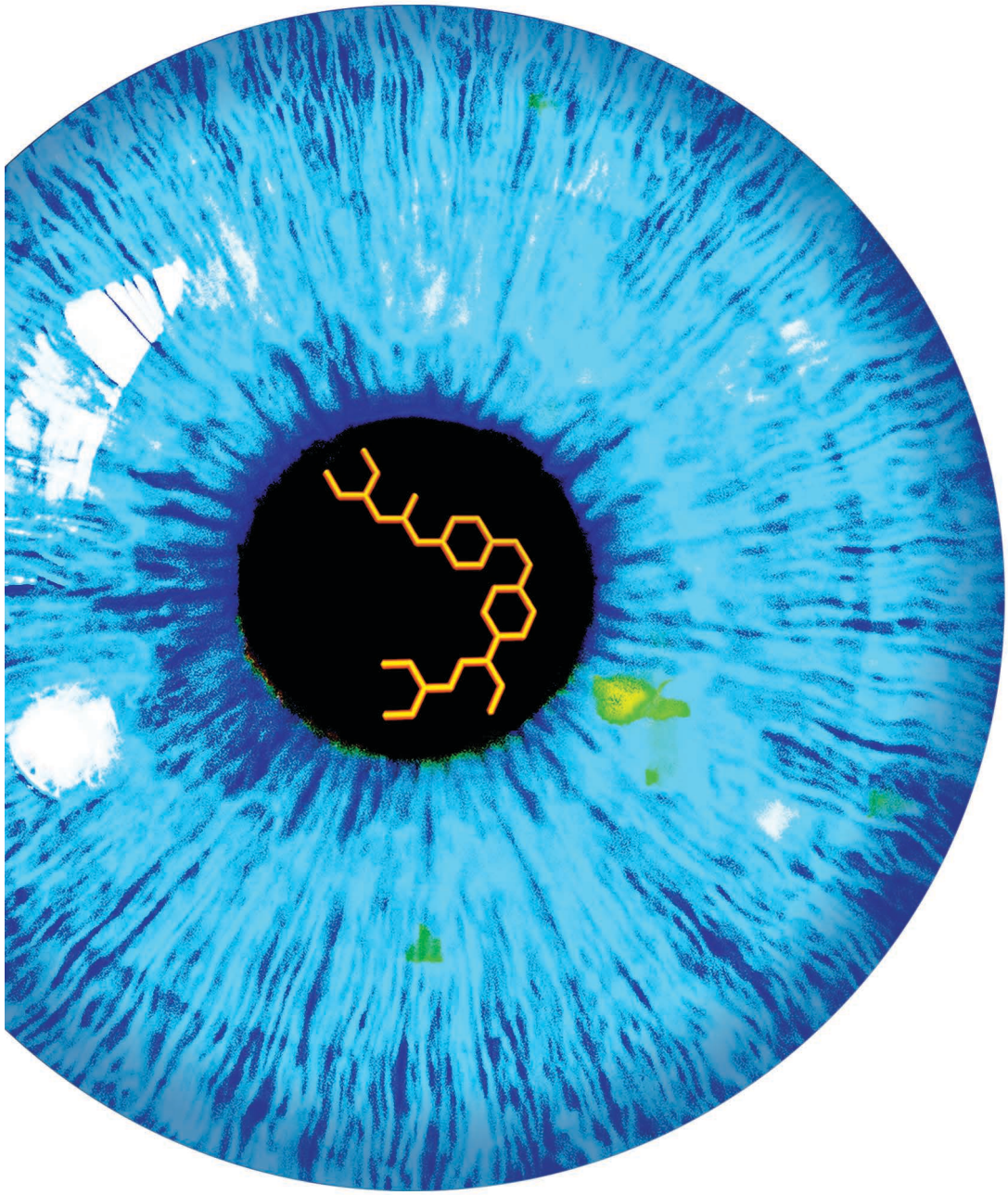

Light-sensitive ligands restore visual function p. 2

APPLICATIONS NOW BEING ACCEPTED

GILEAD SCIENCES
RESEARCH SCHOLARS PROGRAM
IN HEMATOLOGY/ONCOLOGY

Supporting innovative scientific research that will advance knowledge in the field of hematology/oncology, with a focus on hematologic malignancies, that can be either based around a clinical trial with strong correlative science or a laboratory investigation, and provide support for research career development for young researchers in Canada or the United States

Each award will be funded up to USD130,000, to be paid in annual installments of up to USD65,000

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Applications will be reviewed by a Committee of internationally recognized experts in basic and clinical research in the field of hematology/oncology

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JCI This Month

July 2017

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From the Editor

A change in editorship

This issue of the *Journal of Clinical Investigation* marks the transition to a new editorial team from Johns Hopkins University. It is with great humility and excitement that we assume the mantle of the leading translational science journal in the world and the flagship of the American Society for Clinical Investigation.

What do we hope to accomplish in our editorial term? The major priority is the continued communication of world-class, clinically directed fundamental science and cultivating novel ways to transmit this information. We will work with the ASCI leadership to develop the most efficient model for publishing and disseminating the *JCI*.

Arguably my most important task as Editor is the selection of the Editorial Board. We have assembled an extraordinary and accomplished group of Associate Editors from Johns Hopkins. The editorial group has the expertise to cover the breadth of science submitted to the journal and the innovative spirit required to assess the quality and importance of emerging areas. We recognize the challenges of the ever-changing landscape of publishing and will endeavor to meet these challenges head-on.

We believe this an exciting time to be editors of the journal, and there has never been a better opportunity to realize the goals of the *JCI* and ASCI: the timely transmission of scientific information with the goal of improving human health and a celebration of the physician-scientist. We will work tirelessly to this end, and, to paraphrase Churchill, will be easily satisfied only by the very best.

Gordon F. Tomaselli
Editor in Chief, The Journal of Clinical Investigation

To read Dr. Tomaselli's complete editorial, see http://jci.me/95387.

For the full JCI online:
jci.me/127/7

For JCI Insight:
jci.me/insight/2/11
jci.me/insight/2/12

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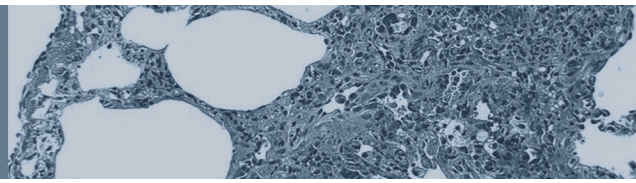
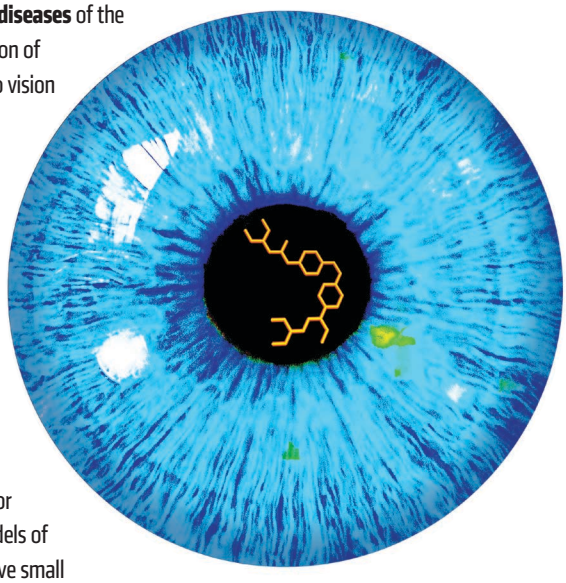


OPHTHALMOLOGY

Light-responsive ligands photosensitize bipolar cells in blind mice



Retinitis pigmentosa and other diseases of the retina cause a gradual degeneration of photoreceptors that progresses to vision loss. Although retinal prosthesis, stem cell transplantation, and gene therapy strategies are in development to reverse blindness, each is associated with safety concerns related to long-term stability. Light-sensitive ligands are an alternative strategy for restoring vision, particularly because the reversibility of a pharmacological approach may be more suitable for clinical application. In mouse models of retinal degeneration, light-sensitive small molecules known as photoswitches have been shown to restore light responses. However, existing photoswitches do not incorporate higher-order retinal circuitry, potentially limiting their ability to restore complex visual function. In this issue of the *JCI*, Laura Laprell et al. characterized diethylamino-azo-diethylamino (DAD), a third-generation photoswitch that is capable of restoring visual function in blind mice. DAD's design enables it to exist in uncharged and charged forms to facilitate delivery across biological barriers while remaining highly soluble. When exposed to blue or white light, DAD efficiently switched from *trans* to *cis* configuration and rapidly reverted to *trans* in darkness. In mice, DAD application restored light responses primarily by photosensitizing bipolar cells, the retinal neurons that receive and integrate input from photoreceptors. DAD's actions through bipolar cells may represent an advantage over previously characterized photoswitches, because utilizing the existing retinal circuitry may permit enhanced visual resolution. The cover shows the DAD photoswitch in light-activated *cis* configuration within an eye. Image credit: Laura Laprell.

Photopharmacological control of bipolar cells restores visual function in blind mice

Laura Laprell, Ivan Tochitsky, Kuldeep Kaur, Michael B. Manookin, Marco Stein, David M. Barber, Christian Schön, Stylianos Michalakis, Martin Biel, Richard H. Kramer, Martin P. Sumser, Dirk Trauner, and Russell N. Van Gelder **http://jci.me/92156**

NEUROSCIENCE

Linking gain-of-function mutations in sodium channel $Na_V1.9$ to pain insensitivity

Gain-of-function mutations in the voltage-dependent sodium channel $Na_V1.9$ can produce both hypersensitivity and insensitivity to pain. The mechanisms that underlie the divergent pathological consequences of these mutations are unclear. Jianying Huang, Carlos Vanoye, and coworkers examined properties of $Na_V1.9$ and the consequences of gain-of-function mutations that produce human pain disorders. Gain-of-function $Na_V1.9$ mutations shifted the voltage dependence of channel activation but not inactivation, resulting in a wider window for sodium conductance. Enhanced sodium conductance evoked a large depolarization of the neuronal resting membrane potential (RMP) and impaired neuronal excitability, consistent with insensitivity to pain. By contrast, less dramatic gains in $Na_V1.9$ function evoked smaller degrees of membrane depolarization, driving enhanced neuronal excitability and pain. This U-shaped relationship provides an explanation for the divergent effects of $Na_V1.9$ mutations in pathological nociception.

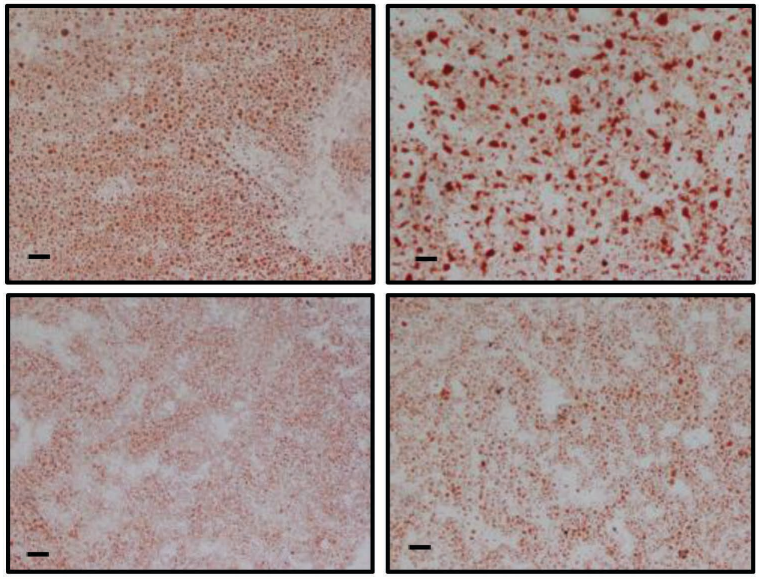
Sodium channel $Na_V1.9$ mutations associated with insensitivity to pain dampen neuronal excitability

Jianying Huang, Carlos G. Vanoye, Alison Cutts, Y. Paul Goldberg, Sulayman D. Dib-Hajj, Charles J. Cohen, Stephen G. Waxman, and Alfred L. George Jr. **http://jci.me/92373**

HEPATOLOGY

Alcohol-related perturbations in intestinal fungi promote liver disease

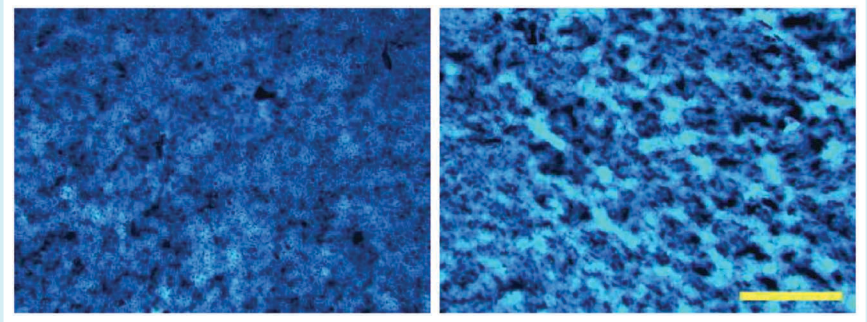
Chronic alcoholism alters gut barrier integrity as well as the composition of the gut microbiome. Although alcoholism contributes to a significant proportion of liver cirrhosis-related deaths, the role of the microbiome, and specifically the fungal commensal, has not been investigated. An-Ming Yang, Tatsuo Inamine, and colleagues demonstrated that long-term alcohol administration increased intestinal fungal populations and plasma levels of the fungal polysaccharide β-glucan in mice. Moreover, nonabsorbable antifungal agents prevented alcohol-induced overgrowth in the intestine and reduced signs of liver disease in these mice (see the accompanying image). Further observations revealed that β-glucan activates the pattern recognition receptor CLEC7A on liver-resident macrophages, leading to IL-1β–induced inflammation. Finally, the researchers found that alcohol-dependent patients lost fungal diversity and exhibited *Candida* overgrowth. The immune response to intestinal fungi correlated with survival in alcohol-dependent patients. Together, these data suggest that targeting commensal fungi is a potential strategy to mitigate alcohol-related liver damage.



Intestinal fungi contribute to development of alcoholic liver disease
An-Ming Yang, Tatsuo Inamine, Katrin Hochrath, Peng Chen, Lirui Wang, Cristina Llorente, Sena Bluemel, Phillipp Hartmann, Jun Xu, Yukinori Koyama, Tatiana Kisseleva, Manolito G. Torralba, Kelvin Moncera, Karen Beeri, Chien-Sheng Chen, Kim Freese, Claus Hellerbrand, Serene M.L. Lee, Hal M. Hoffman, Wajahat Z. Mehal, Guadalupe Garcia-Tsao, Ece A. Mutlu, Ali Keshavarzian, Gordon D. Brown, Samuel B. Ho, Ramon Bataller, Peter Stärkel, Derrick E. Fouts, and Bernd Schnabl **http://jci.me/90562**

ChREBP protects against fructose-induced hepatotoxicity by restraining cholesterol biosynthesis

There are no approved therapies for nonalcoholic fatty liver disease (NAFLD), a progressive metabolic disorder that advances from hepatic steatosis to nonalcoholic steatohepatitis (NASH) and cirrhosis. NASH-like liver injury was initially linked to diets high in saturated fat, but it was also recently associated with high-fructose diets. Noting that the lipogenic transcription factor carbohydrate response element–binding protein (ChREBP)regulates the expression of several enzymes in the pathway that converts fructose into fatty acids in the liver, Deqiang Zhang and labmates examined the role of ChREBP in mediating the effects of a high-fructose diet in mice. Although ChREBP expression promoted de novo lipogenesis in response to a high-fructose diet, it also mitigated NASH and liver injury. Further investigation revealed a pathway through which ChREBP limits hepatic cholesterol biosynthesis and associated apoptotic responses (see the associated image). In the accompanying Commentary, Angela Hall and Brian Finck unpack the finding that diet-induced increases in cholesterol biosynthesis initiate liver injury that can progress to NASH.



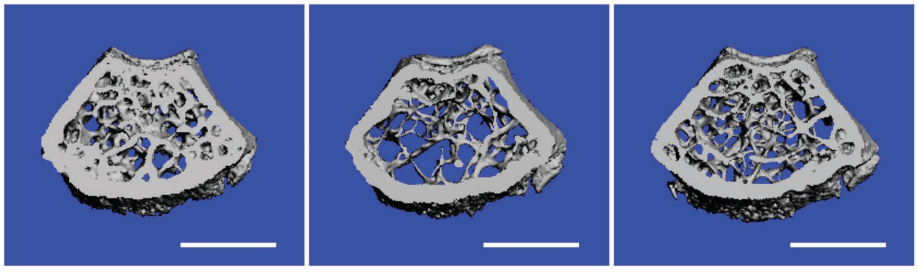
Lipogenic transcription factor ChREBP mediates fructose-induced metabolic adaptations to prevent hepatotoxicity
Deqiang Zhang, Xin Tong, Kyle VanDommelen, Neil Gupta, Kenneth Stamper, Graham F. Brady, Zhuoxian Meng, Jiandie Lin, Liangyou Rui, M. Bishr Omary, and Lei Yin **http://jci.me/89934**

▶ Related Commentary
ChREBP refines the hepatic response to fructose to protect the liver from injury
Angela M. Hall and Brian N. Finck **http://jci.me/95008**

BONE BIOLOGY

MYC-dependent metabolic reprogramming regulates osteoclastogenesis and bone loss

Osteoporosis results from imbalances between bone formation and bone resorption. The latter process is mediated by osteoclasts, which are myeloid lineage cells that are activated by RANKL/RANK signaling. Seyeon Bae, Min Joon Lee, and coworkers have demonstrated a key role for the transcription factor MYC in regulating RANKL-mediated osteoclast activation. Selectively deleting Myc in osteoclasts led to increased bone mass and decreased osteoclastogenesis in mice. Using transcriptomic and gene set enrichment analyses, the researchers discovered that MYC interacts with the promoter of nuclear receptor ERRα to regulate oxidative metabolism in osteoclast progenitors. In a mouse model of estrogen deficiency–driven osteoporosis, disrupting the MYC/ERRα axis mitigated pathological bone loss (see the associated image). In the accompanying Commentary, Joseph Lorenzo discusses the possibility of targeting the MYC/ERRα pathway as an osteoclast-focused approach to treating osteoporosis.

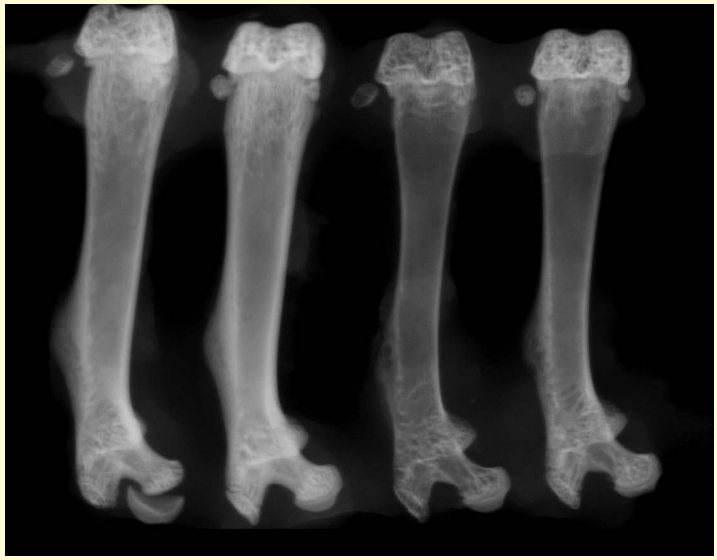


MYC-dependent oxidative metabolism regulates osteoclastogenesis via nuclear receptor ERRα
Seyeon Bae, Min Joon Lee, Se Hwan Mun, Eugenia G. Giannopoulou, Vladimir Yong-Gonzalez, Justin R. Cross, Koichi Murata, Vincent Giguère, Marjolein van der Meulen, and Kyung-Hyun Park-Min http://jci.me/89935

▶ Related Commentary
The many ways of osteoclast activation
Joseph Lorenzo http://jci.me/94606

Osteocyte-derived WNT1 signaling is a key driver of osteoblast activity

Osteocytes were initially considered to be quiescent members of the bone matrix, but current understanding suggests an active role in bone homeostasis. Osteocytes secrete sclerostin, which inhibits the Wnt signaling pathway to downregulate the differentiation of bone-forming osteoblasts. Though Wnt is also involved in bone homeostasis, its cellular source is unclear. A study conducted by Kyu Sang Joeng, Yi-Chien Lee, and labmates identifies osteocyte-derived WNT1 signaling as a critical driver of osteoblast activity. In mice, osteocyte-selective ablation of WNT1 decreased bone formation and increased fracture rates. Conversely, WNT1 overexpression enhanced osteoblast differentiation and bone mineralization in an mTOR-dependent manner. In a WNT1 loss-of-function model, loss of tuberous sclerosis 1 (TSC1), a negative regulator of mTOR, or treatment with an anti-sclerostin antibody improved bone mineralization and formation (see the associated image). In the accompanying Commentary, Frank Rauch links osteocyte-intrinsic Wnt signaling to potential strategies for treating WNT1-related bone diseases.



Osteocyte-specific WNT1 regulates osteoblast function during bone homeostasis
Kyu Sang Joeng, Yi-Chien Lee, Joohyun Lim, Yuqing Chen, Ming-Ming Jiang, Elda Munivez, Catherine Ambrose, and Brendan H. Lee http://jci.me/92617

▶ Related Commentary
The brains of the bones: how osteocytes use WNT1 to control bone formation
Frank Rauch http://jci.me/95386

IMMUNOLOGY

Excessive pyruvate metabolism confers immunosuppressive properties to macrophages

Reactivation of varicella zoster virus (VZV) causes shingles in adults and is typically associated with an age-related decline in T cell immunity. Older adults with coronary artery disease (CAD) are particularly at risk for VZV reactivation. Although atherosclerosis progression has been linked to pathogenic immune responses, the mechanisms underlying CAD-linked immunodeficiency are unclear. Ryu Watanabe, Tsuyoshi Shirai, and colleagues observed that macrophages derived from patients with CAD promote defective T cell immunity by suppressing T cell activation and proliferation. Through a series of mechanistic experiments, they determined that excessive pyruvate in CAD macrophages upregulated expression of the immunosuppressive ligand programmed death ligand–1 (PD-L1), leading to aberrant activation of the PD-1 checkpoint on T cells. These findings imply that strategies to correct metabolic dysregulation in immune cells may provide an opportunity to restore adaptive immunity in CAD-affected individuals.

Pyruvate controls the checkpoint inhibitor PD-L1 and suppresses T cell immunity

Ryu Watanabe, Tsuyoshi Shirai, Hong Namkoong, Hui Zhang, Gerald J. Berry, Barbara B. Wallis, Benedikt Schaefgen, David G. Harrison, Jennifer A. Tremmel, John C. Giacomini, Jörg J. Goronzy, and Cornelia M. Weyand **http://jci.me/92167**

Heparanase guides NK cell surveillance of tumors

NK cells play an important role in controlling cancer metastasis. However, in solid tumors, the extracellular matrix (ECM) creates an immune barrier that is difficult for NK cells to cross, limiting their antitumor activity. Tumor cells contend with ECM by expressing heparanase, an enzyme that degrades ECM to allow tumor cell proliferation and vascularization. Eva Putz and colleagues have demonstrated that NK cells also depend on heparanase to mediate their recruitment to the site of tumors and metastases. Although specific loss of heparanase in NK cells did not affect their development and maintenance in tissues, it impaired NK cell antitumor activity against chemically induced and transplanted carcinomas. In addition, NK cell–specific heparanase deficiency compromised the efficacy of a combined checkpoint blockade immunotherapy against lung metastases. Together, these results identify heparanase as an important facilitator of the antitumor activity of NK cells.

NK cell heparanase controls tumor invasion and immune surveillance

Eva M. Putz, Alyce J. Mayfosh, Kevin Kos, Deborah S. Barkauskas, Kyohei Nakamura, Liam Town, Katharine J. Goodall, Dean Y. Yee, Ivan K.H. Poon, Nikola Baschuk, Fernando Souza-Fonseca-Guimaraes, Mark D. Hulett, and Mark J. Smyth **http://jci.me/92958**

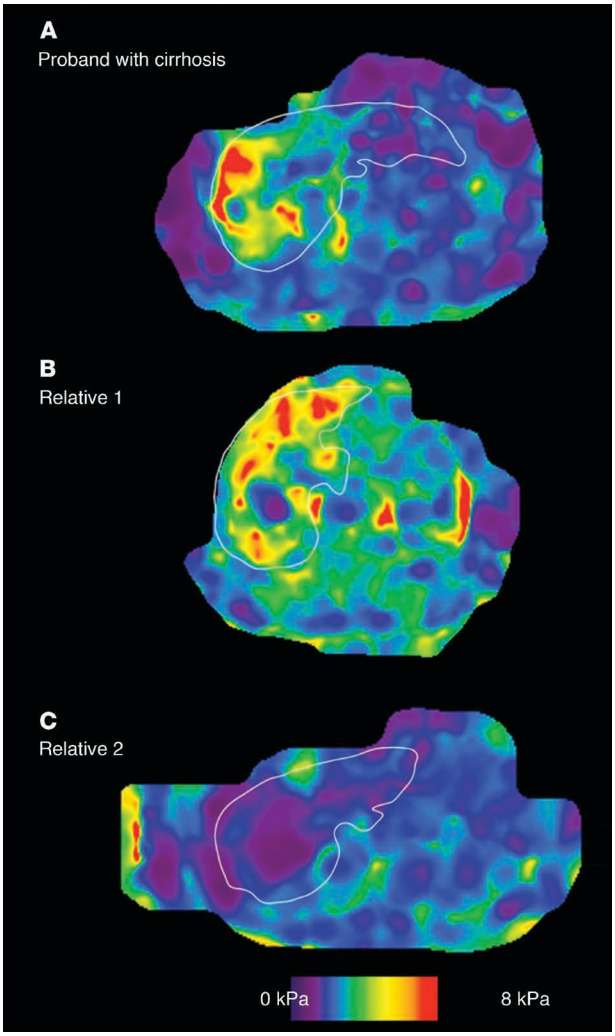
AIDS/HIV

Th1 cells harboring clonally expanded and replication-competent HIV-1 maintain a viral reservoir

HIV-1 infection remains incurable due to the virus's persistence in a long-lived reservoir of CD4$^+$ T cells. Interrupting combination antiretroviral therapy (cART) can provoke rebound viremia that is driven by the presence of these latently infected cells. Guinevere Lee, Nina Orlova-Fink, and colleagues interrogated CD4$^+$ T cells from cART-treated, HIV-1–positive individuals to better understand the mechanisms that support the remarkable long-term stability of latent infection. Deep sequencing of HIV-1 DNA from sorted subsets of CD4$^+$ T subpopulations revealed that Th1-polarized CD4$^+$ T cells are disproportionally enriched in near full-length and replication-competent proviral sequences and can amplify viral reservoir cells through clonal proliferation. In the accompanying Commentary, Kyungyoon Kwon and Robert Siliciano explain the groundwork this study provides for developing strategies to interrupt clonal proliferation and decrease the latent HIV-1 viral reservoir.

Clonal expansion of genome-intact HIV-1 in functionally polarized Th1 CD4$^+$ T cells
Guinevere Q. Lee, Nina Orlova-Fink, Kevin Einkauf, Fatema Z. Chowdhury, Xiaoming Sun, Sean Harrington, Hsiao-Hsuan Kuo, Stephane Hua, Hsiao-Rong Chen, Zhengyu Ouyang, Kavidha Reddy, Krista Dong, Thumbi Ndung'u, Bruce D. Walker, Eric S. Rosenberg, Xu G. Yu, and Mathias Lichterfeld
http://jci.me/93289

▶ Related Commentary
HIV persistence: clonal expansion of cells in the latent reservoir
Kyungyoon J. Kwon and Robert F. Siliciano
http://jci.me/95329



CLINICAL MEDICINE

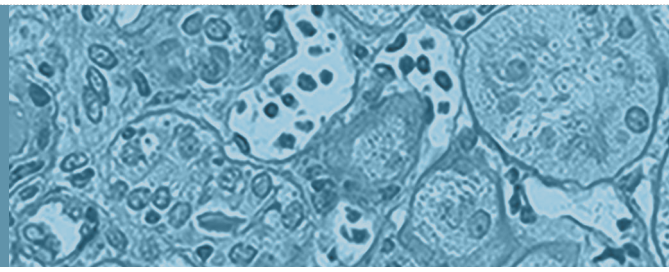
Cirrhosis accompanying nonalcoholic fatty liver disease increases familial fibrosis risk

Nonalcoholic fatty liver disease (NAFLD) is characterized by abnormal accumulation of hepatic fat deposits. NAFLD presenting with cirrhosis predicts poor patient outcomes, indicating a substantially higher risk of mortality due to liver disease. A prospective clinical trial led by Rohit Loomba assessed whether first-degree relatives of individuals with NAFLD and cirrhosis are at higher risk of developing advanced fibrosis. They quantified fibrosis using magnetic resonance elastography in 26 individuals with NAFLD with cirrhosis and 39 first-degree relatives (see the accompanying image). Compared with the first-degree relatives of healthy controls, first-degree relatives of individuals with NAFLD and cirrhosis were 12 times more likely to develop advanced fibrosis. These findings indicate that screening for advanced fibrosis may be beneficial for the first-degree family members of individuals with cirrhosis due to NAFLD.

Nonalcoholic fatty liver disease with cirrhosis increases familial risk for advanced fibrosis
Cyrielle Caussy, Meera Soni, Jeffrey Cui, Ricki Bettencourt, Nicholas Schork, Chi-Hua Chen, Mahdi Al Ikhwan, Shirin Bassirian, Sandra Cepin, Monica P. Gonzalez, Michel Mendler, Yuko Kono, Irine Vodkin, Kristin Mekeel, Jeffrey Haldorson, Alan Hemming, Barbara Andrews, Joanie Salotti, Lisa Richards, David A. Brenner, Claude B. Sirlin, Rohit Loomba, and the Familial NAFLD Cirrhosis Research Consortium
http://jci.me/93465

JCI Review Series

Transplantation



Taming the immune system to improve transplantation

Organ and tissue transplantation are frequently life-extending procedures for patients with end-stage organ disease or hematological malignancies; however, the success of transplantation of organs and tissues to a recipient from a genetically nonidentical donor is limited by immune-mediated complications, including rejection, graft dysfunction, graft-versus-host disease, and the side effects of preventing rejection. Despite over 100 years of research in this area, we are just now beginning to develop an in-depth understanding of the immune mechanisms that determine the success of allotransplantation. A detailed understanding of transplantation immunology will allow for better selection of donor/recipient pairs, the development of novel therapeutic strategies, and, ultimately, better outcomes. Reviews in this series explore the role of cytokines in both acute and chronic graft-versus-host disease; the effects of sterile inflammation, danger signals, and the inflammasome in solid organ transplantation; the mechanisms of humoral and cellular rejection; cell-based therapies to combat rejection and transplantation-associated infections; and the effects of both host-intrinsic and -extrinsic factors in transplantation outcomes.

Scott M. Palmer, MD, *is Professor of Medicine, Duke University Medical Center, and Director of Pulmonary Research at the Duke Clinical Research Institute. His primary research interests are centered on the areas of bronchiolitis obliterans, lung transplantation, and advanced lung disease. He made the important observation that variations in innate pattern recognition receptors regulate lung rejection, thereby establishing the clinical importance of innate mechanisms in solid organ transplant rejection. His work has also highlighted the adverse effects of cytomegalovirus (CMV) infection after lung transplantation. As a result, he led a multicenter randomized clinical trial that established a new and more effective clinical standard of care to prevent the development of CMV infection. He continues to leverage translational human studies and rodent models to better understand the mechanisms that lead to lung rejection and develop clinically relevant approaches to modulate these processes and improve transplant outcomes.*

Jonathan S. Serody, MD, *is the Elizabeth Thomas Professor of Medicine at the University of North Carolina at Chapel Hill and the Director of the Immunotherapy Program of the Lineberger Comprehensive Cancer Center. His research focuses on how cellular migration and different T cell subsets affect transplantation and tumor biology. Dr. Serody's laboratory was the first to describe a role for chemokines in the biology of acute and chronic graft-versus-host disease (GVHD), and this work has led to the development of CCR5 inhibitors to prevent acute GVHD clinically. Currently his laboratory focuses on epigenetic modulation and its role in the adaptive immune response after stem cell transplantation, the role of innate lymphoid cells in the initiation of GVHD, and the biology of immunosuppressive populations of T cells and myeloid cells and their role in tumor growth and dissemination.*

JCI Current research articles

AIDS/HIV

Clonal expansion of genome-intact HIV-1 in functionally polarized Th1 CD4+ T cells ▶ p. 6

Guinevere Q. Lee, Nina Orlova-Fink, Kevin Einkauf, Fatema Z. Chowdhury, Xiaoming Sun, Sean Harrington, Hsiao-Hsuan Kuo, Stephane Hua, Hsiao-Rong Chen, Zhengyu Ouyang, Kavidha Reddy, Krista Dong, Thumbi Ndung'u, Bruce D. Walker, Eric S. Rosenberg, Xu G. Yu, and Mathias Lichterfeld http://jci.me/93289

BONE BIOLOGY

MYC-dependent oxidative metabolism regulates osteoclastogenesis via nuclear receptor ERRα ▶ p. 4

Seyeon Bae, Min Joon Lee, Se Hwan Mun, Eugenia G. Giannopoulou, Vladimir Yong-Gonzalez, Justin R. Cross, Koichi Murata, Vincent Giguère, Marjolein van der Meulen, and Kyung-Hyun Park-Min http://jci.me/89935

Ubiquitin ligase RNF146 coordinates bone dynamics and energy metabolism

Yoshinori Matsumoto, Jose La Rose, Melissa Lim, Hibret A. Adissu, Napoleon Law, Xiaohong Mao, Feng Cong, Paula Mera, Gerard Karsenty, David Goltzman, Adele Changoor, Lucia Zhang, Megan Stajkowski, Marc D. Grynpas, Carsten Bergmann, and Robert Rottapel http://jci.me/92233

Osteocyte-specific WNT1 regulates osteoblast function during bone homeostasis ▶ p. 4

Kyu Sang Joeng, Yi-Chien Lee, Joohyun Lim, Yuqing Chen, Ming-Ming Jiang, Elda Munivez, Catherine Ambrose, and Brendan H. Lee http://jci.me/92617

CELL BIOLOGY

Cell-penetrating peptides selectively targeting SMAD3 inhibit profibrotic TGF-β signaling

Jeong-Han Kang, Mi-Yeon Jung, Xueqian Yin, Mahefatiana Andrianifahanana, Danielle M. Hernandez, and Edward B. Leof http://jci.me/88696

CLINICAL MEDICINE

Nonalcoholic fatty liver disease with cirrhosis increases familial risk for advanced fibrosis ▶ p. 6

Cyrielle Caussy, Meera Soni, Jeffrey Cui, Ricki Bettencourt, Nicholas Schork, Chi-Hua Chen, Mahdi Al Ikhwan, Shirin Bassirian, Sandra Cepin, Monica P. Gonzalez, Michel Mendler, Yuko Kono, Irine Vodkin, Kristin Mekeel, Jeffrey Haldorson, Alan Hemming, Barbara Andrews, Joanie Salotti, Lisa Richards, David A. Brenner, Claude B. Sirlin, Rohit Loomba, and the Familial NAFLD Cirrhosis Research Consortium http://jci.me/93465

ENDOCRINOLOGY

Neuropeptide FF increases M2 activation and self-renewal of adipose tissue macrophages

Syed F. Hassnain Waqas, Anh Cuong Hoang, Ya-Tin Lin, Grace Ampem, Hind Azegrouz, Lajos Balogh, Julianna Thuróczy, Jin-Chung Chen, Ivan C. Gerling, Sorim Nam, Jong-Seok Lim, Juncal Martinez-Ibañez, José T. Real, Stephan Paschke, Raphaëlle Quillet, Safia Ayachi, Frédéric Simonin, E. Marion Schneider, Jacqueline A. Brinkman, Dudley W. Lamming, Christine M. Seroogy, and Tamás Röszer http://jci.me/90152

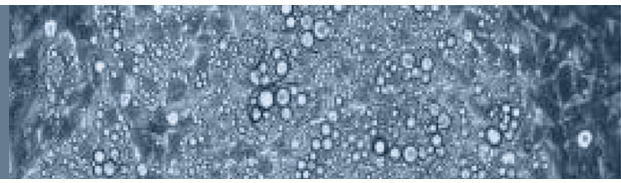
A cullin 4B-RING E3 ligase complex fine-tunes pancreatic δ cell paracrine interactions

Qing Li, Min Cui, Fan Yang, Na Li, Baichun Jiang, Zhen Yu, Daolai Zhang, Yijing Wang, Xibin Zhu, Huili Hu, Pei-Shan Li, Shang-Lei Ning, Si Wang, Haibo Qi, Hechen Song, Dongfang He, Amy Lin, Jingjing Zhang, Feng Liu, Jiajun Zhao, Ling Gao, Fan Yi, Tian Xue, Jin-Peng Sun, Yaoqin Gong, and Xiao Yu
http://jci.me/91348

HEPATOLOGY

Lipogenic transcription factor ChREBP mediates fructose-induced metabolic adaptations to prevent hepatotoxicity ▶ p. 3

Deqiang Zhang, Xin Tong, Kyle VanDommelen, Neil Gupta, Kenneth Stamper, Graham F. Brady, Zhuoxian Meng, Jiandie Lin, Liangyou Rui, M. Bishr Omary, and Lei Yin http://jci.me/89934



Intestinal fungi contribute to development of alcoholic liver disease ▶ p. 3

An-Ming Yang, Tatsuo Inamine, Katrin Hochrath, Peng Chen, Lirui Wang, Cristina Llorente, Sena Bluemel, Phillip Hartmann, Jun Xu, Yukinori Koyama, Tatiana Kisseleva, Manolito G. Torralba, Kelvin Moncera, Karen Beeri, Chien-Sheng Chen, Kim Freese, Claus Hellerbrand, Serene M.L. Lee, Hal M. Hoffman, Wajahat Z. Mehal, Guadalupe Garcia-Tsao, Ece A. Mutlu, Ali Keshavarzian, Gordon D. Brown, Samuel B. Ho, Ramon Bataller, Peter Stärkel, Derrick E. Fouts, and Bernd Schnabl http://jci.me/90562

Kinase-independent functions of RIPK1 regulate hepatocyte survival and liver carcinogenesis

Trieu-My Van, Apostolos Polykratis, Beate Katharina Straub, Vangelis Kondylis, Nikoletta Papadopoulou, and Manolis Pasparakis http://jci.me/92508

IMMUNOLOGY

Tregs restrain dendritic cell autophagy to ameliorate autoimmunity

Themis Alissafi, Aggelos Banos, Louis Boon, Tim Sparwasser, Alessandra Ghigo, Kajsa Wing, Dimitrios Vassilopoulos, Dimitrios Boumpas, Triantafyllos Chavakis, Ken Cadwell, and Panayotis Verginis http://jci.me/92079

Pyruvate controls the checkpoint inhibitor PD-L1 and suppresses T cell immunity ▶ p. 5

Ryu Watanabe, Tsuyoshi Shirai, Hong Namkoong, Hui Zhang, Gerald J. Berry, Barbara B. Wallis, Benedikt Schaefgen, David G. Harrison, Jennifer A. Tremmel, John C. Giacomini, Jörg J. Goronzy, and Cornelia M. Weyand http://jci.me/92167

A therapeutic T cell receptor mimic antibody targets tumor-associated PRAME peptide/HLA-I antigens

Aaron Y. Chang, Tao Dao, Ron S. Gejman, Casey A. Jarvis, Andrew Scott, Leonid Dubrovsky, Melissa D. Mathias, Tatyana Korontsvit, Victoriya Zakhaleva, Michael Curcio, Ronald C. Hendrickson, Cheng Liu, and David A. Scheinberg http://jci.me/92335

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Lysine methyltransferase SMYD2 promotes cyst growth in autosomal dominant polycystic kidney disease

Linda Xiaoyan Li, Lucy X. Fan, Julie Xia Zhou, Jared J. Grantham, James P. Calvet, Julien Sage, and Xiaogang Li http://jci.me/90921

Macrolides selectively inhibit mutant KCNJ5 potassium channels that cause aldosterone-producing adenoma

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NEUROSCIENCE

Arcuate neuropeptide Y inhibits sympathetic nerve activity via multiple neuropathways

Zhigang Shi, Christopher J. Madden, and Virginia L. Brooks http://jci.me/92008

CRISPR/Cas9-mediated gene editing ameliorates neurotoxicity in mouse model of Huntington's disease

Su Yang, Renbao Chang, Huiming Yang, Ting Zhao, Yan Hong, Ha Eun Kong, Xiaobo Sun, Zhaohui Qin, Peng Jin, Shihua Li, and Xiao-Jiang Li http://jci.me/92087

Sodium channel $Na_v1.9$ mutations associated with insensitivity to pain dampen neuronal excitability ▶ p. 2

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JCI Current research articles

ONCOLOGY

Genetic regulation of the RUNX transcription factor family has antitumor effects

Ken Morita, Kensho Suzuki, Shintaro Maeda, Akihiko Matsuo, Yoshihide Mitsuda, Chieko Tokushige, Gengo Kashiwazaki, Junichi Taniguchi, Rina Maeda, Mina Noura, Masahiro Hirata, Tatsuki Kataoka, Ayaka Yano, Yoshimi Yamada, Hiroki Kiyose, Mayu Tokumasu, Hidemasa Matsuo, Sunao Tanaka, Yasushi Okuno, Manabu Muto, Kazuhito Naka, Kosei Ito, Toshio Kitamura, Yasufumi Kaneda, Paul P. Liu, Toshikazu Bando, Souichi Adachi, Hiroshi Sugiyama, and Yasuhiko Kamikubo
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OPHTHALMOLOGY

Targeting neuronal gap junctions in mouse retina offers neuroprotection in glaucoma

Abram Akopian, Sandeep Kumar, Hariharasubramanian Ramakrishnan, Kaushambi Roy, Suresh Viswanathan, and Stewart A. Bloomfield
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Photopharmacological control of bipolar cells restores visual function in blind mice ▶ p. 2

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PULMONOLOGY

Calcium-binding protein S100A4 confers mesenchymal progenitor cell fibrogenicity in idiopathic pulmonary fibrosis

Hong Xia, Adam Gilbertsen, Jeremy Herrera, Emilian Racila, Karen Smith, Mark Peterson, Timothy Griffin, Alexey Benyumov, Libang Yang, Peter B. Bitterman, and Craig A. Henke **http://jci.me/90832**

TRANSPLANTATION

Differential requirements for myeloid leukemia IFN-γ conditioning determine graft-versus-leukemia resistance and sensitivity

Catherine Matte-Martone, Jinling Liu, Meng Zhou, Maria Chikina, Douglas R. Green, John T. Harty, and Warren D. Shlomchik **http://jci.me/85736**

VASCULAR BIOLOGY

RASA1 regulates the function of lymphatic vessel valves in mice

Philip E. Lapinski, Beth A. Lubeck, Di Chen, Abbas Doosti, Scott D. Zawieja, Michael J. Davis, and Philip D. King **http://jci.me/89607**

VIROLOGY

Glutamine supplementation suppresses herpes simplex virus reactivation

Kening Wang, Yo Hoshino, Kennichi Dowdell, Marta Bosch-Marce, Timothy G. Myers, Mayra Sarmiento, Lesley Pesnicak, Philip R. Krause, and Jeffrey I. Cohen
http://jci.me/88990

AIDS/HIV

Type I interferons: a double-edged sword in HIV-1 infection and pathogenesis

Type I interferons (IFN-Is) play a critical role in controlling viral infections, but their precise role in HIV-1 pathogenesis is not clear. In order to clarify the role of IFN-Is in chronic HIV-1 infection, Liang Cheng and colleagues examined the effects of an IFN-I receptor–blocking (IFNAR1-blocking) mAb in a humanized mouse model of persistent HIV-1 infection. HIV-1 infection in humanized mice led to persistent induction of IFN-Is and IFN-stimulated genes, associated with human T cell depletion. Administration of the IFNAR1-blocking mAb enhanced viral replication and rescued both the number and function of human T cells, including HIV-1–specific T cells. These results suggest that while IFN-I signaling suppresses HIV-1 replication during chronic infection, it also plays a detrimental role by inducing human T cell depletion and impairing HIV-1–specific T cell functions. Therapeutic strategies to disrupt IFN-I signaling could potentially enhance anti-HIV immune responses in HIV-1–infected patients.

Type I interferons suppress viral replication but contribute to T cell depletion and dysfunction during chronic HIV-1 infection

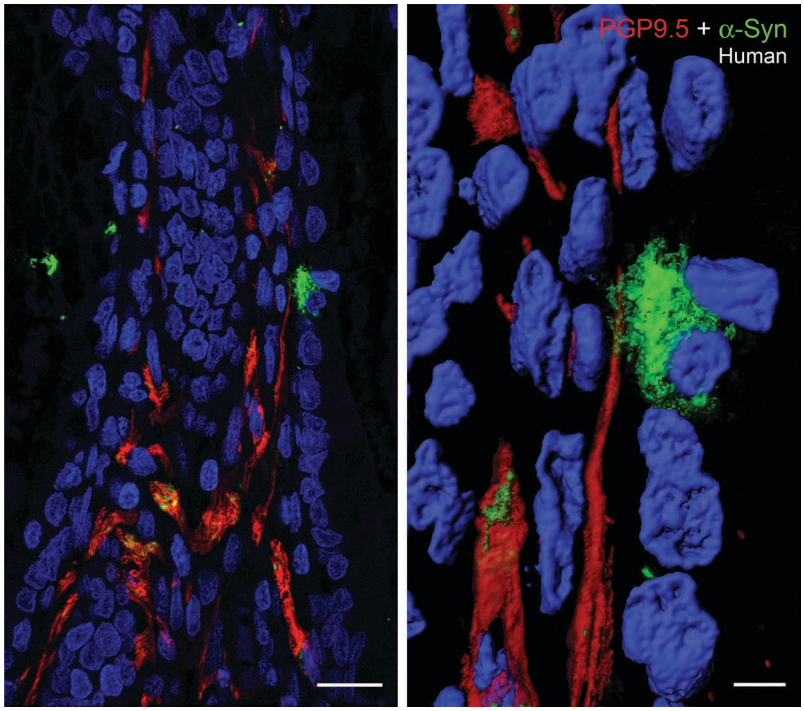
Liang Cheng, Haisheng Yu, Guangming Li, Feng Li, Jianping Ma, Jingyun Li, Liqun Chi, Liguo Zhang, and Lishan Su

http://jci.me/94366

GASTROENTEROLOGY

A gut feeling about α-synuclein in Parkinson's disease

Parkinson's disease (PD) is a progressive neurodegenerative disorder that is characterized by intracellular α-synuclein aggregates, known as Lewy bodies. Patients with PD frequently have gastrointestinal symptoms, and there is clinical evidence that misfolded α-synuclein appears in the enteric nerves of the digestive tract before it is detectable in the brain. Rashmi Chandra and colleagues report that α-synuclein is expressed in both mouse and human enteroendocrine cells (EECs), gut epithelial cells that convey sensory information from the gut to the enteric nervous system. Moreover, α-synuclein–containing EECs were directly connected to gut nerves via their basolateral surface (see the accompanying image; enteric nerves are in red, α-synuclein–positive EECs are in green). These findings identify a previously unrecognized location in which PD-associated changes to α-synuclein may occur and suggest that environmental influences in the gut that induce misfolded α-synuclein in the gut epithelium may spread to the enteric nervous system and then to the CNS.



α-Synuclein in gut endocrine cells and its implications for Parkinson's disease

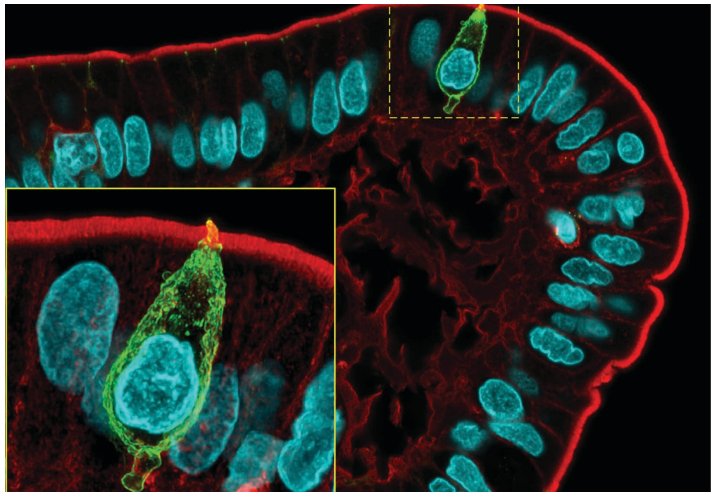
Rashmi Chandra, Annie Hiniker, Yien-Ming Kuo, Robert L. Nussbaum, and Rodger A. Liddle

http://jci.me/92295

TECHNICAL ADVANCE

Multiplex immunofluorescence reveals intestinal tuft cell heterogeneity and dynamics

Intestinal tuft cells are rare, poorly understood intestinal epithelial chemosensory cells that play a role in the type 2 immune response to helminth infection. Eliot McKinley and colleagues developed a multiplex immunofluorescence platform that allows iterative staining with over 60 different antibodies in a single tissue section, to perform a comprehensive analysis of tuft cell number, distribution, and protein expression profiles in the mouse small intestine and colon in different anatomical locations and under physiological perturbations. Protein expression analyses revealed multiple tuft cell subsets and uncovered two new intestinal tuft cell markers, HOP homeobox (HOPX) and tyrosine 1068-phosphorylated EGF receptor; the latter was also identified in human intestine (see the accompanying image). Notably, tuft cell numbers and protein expression profiles were altered during fasting and refeeding and after the introduction of microbiota in germ-free mice, providing a framework for future studies of intestinal tuft cells.



Optimized multiplex immunofluorescence single-cell analysis reveals tuft cell heterogeneity
Eliot T. McKinley, Yunxia Sui, Yousef Al-Kofahi, Bryan A. Millis, Matthew J. Tyska, Joseph T. Roland, Alberto Santamaria-Pang, Christina L. Ohland, Christian Jobin, Jeffrey L. Franklin, Ken S. Lau, Michael J. Gerdes, and Robert J. Coffey
http://jci.me/93487

CLINICAL TRIALS

Dissecting the genetics of the placebo effect

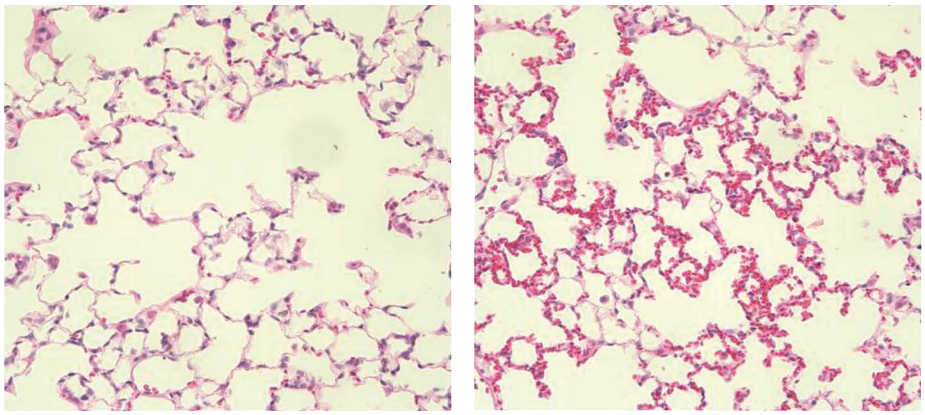
Placebos have long been used as a control treatment in clinical studies of new therapies. The placebo effect is a phenomenon wherein patients given an inactive treatment experience perceived or actual improvement in a medical condition. Recent clinical studies have suggested that the placebo effect has a physiological basis, leading Rui-Sheng Wang and colleagues to try to identify genome-related mediators that may affect the placebo response. Using a seed-connector algorithm, Wang and colleagues developed a "placebome" module consisting of placebo-modulated "seed" proteins and a network of interactors in the comprehensive protein-protein interaction network. They validated the placebome in a large cohort of the Women's Genome Health Study (WGHS) and found that the placebome is enriched for genes whose SNPs were associated with outcomes in the placebo arm of the trial. These findings identify genetic components that underlie the susceptibility of different diseases to the placebo response and suggest that the strength of the placebo response could be predicted and accounted for in clinical trials.

Network analysis of the genomic basis of the placebo effect
Rui-Sheng Wang, Kathryn T. Hall, Franco Giulianini, Dani Passow, Ted J. Kaptchuk, and Joseph Loscalzo **http://jci.me/93911**

PULMONOLOGY

Mechanical ventilation–induced lung injury is exacerbated by zinc deficiency

Mechanical ventilation (MV) is necessary to support patients with acute lung injury, but MV itself can exacerbate lung injury by triggering responses to mechanical stress. Francis Boudreault and colleagues subjected cultured human cells and mouse lungs to stretch-induced mechanical stress and found that it induces expression of metallothionein, a molecule that is critical for zinc homeostasis. Mice lacking metallothionein exhibited worse ventilator-induced lung injury compared with their WT counterparts (see the accompanying image), and ventilator-induced lung injury was also exacerbated in WT mice with dietary zinc deficiency. Moreover, zinc levels were lower in plasma collected from patients with acute respiratory distress syndrome (ARDS) compared with healthy controls and ICU patients without ARDS. These studies suggest that zinc and metallothionein may be therapeutic targets to protect patients requiring MV.

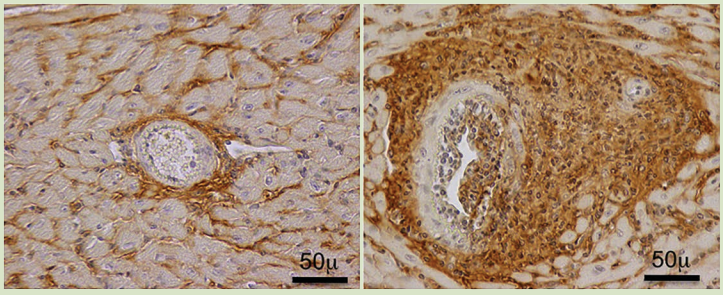


Zinc deficiency primes the lung for ventilator-induced injury
Francis Boudreault, Miguel Pinilla-Vera, Joshua A. Englert, Alvin T. Kho, Colleen Isabelle, Antonio J. Arciniegas, Diana Barragan-Bradford, Carolina Quintana, Diana Amador-Munoz, Jiazhen Guan, Kyoung Moo Choi, MICU Registry, Lynette Sholl, Shelley Hurwitz, Daniel J. Tschumperlin, and Rebecca M. Baron **http://jci.me/86507**

TRANSPLANTATION

Cardiac allograft–specific CD4$^+$ T cells secrete adiponectin to modulate macrophage activity

Adiponectin is a pleiotropic cytokine that modulates many aspects of cardiac and vascular inflammation. While adiponectin is known to be secreted by adipocytes and other parenchymal cells, Sreedevi Danturti and colleagues found that immune cells also secrete adiponectin. Using a model of cardiac transplant–associated chronic arterial inflammation in WT and adiponectin-deficient mice, Danturti and colleagues showed that donor antigen–specific CD4$^+$ T cells from the transplant recipient migrate into the allograft and produce adiponectin locally. Importantly, donor adiponectin deficiency increased macrophage infiltration, modulated macrophage cytokine production, and altered extracellular matrix remodeling, increasing hyaluronan deposition (see the accompanying image). These studies establish T cells as a source of adiponectin that regulates transplant-associated arterial inflammation.



CD4$^+$ T lymphocytes produce adiponectin in response to transplants
Sreedevi Danturti, Karen S. Keslar, Leah R. Steinhoff, Ran Fan, Nina Dvorina, Anna Valujskikh, Robert L. Fairchild, and William M. Baldwin III
http://jci.me/89641

Allergen-encoding bone marrow transfer inactivates allergic T cell responses, alleviating airway inflammation

Jane AL-Kouba, Andrew N. Wilkinson, Malcolm R. Starkey, Rajeev Rudraraju, Rhiannon B. Werder, Xiao Liu, Soi-Cheng Law, Jay C. Horvat, Jeremy F. Brooks, Geoffrey R. Hill, Janet M. Davies, Simon Phipps, Philip M. Hansbro, and Raymond J. Steptoe **http://jci.me/85742**

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Long-term culture of human liver tissue with advanced hepatic functions

Soon Seng Ng, Anming Xiong, Khanh Nguyen, Marilyn Masek, Da Yoon No, Menashe Elazar, Eyal Shteyer, Mark A. Winters, Amy Voedisch, Kate Shaw, Sheikh Tamir Rashid, Curtis W. Frank, Nam Joon Cho, and Jeffrey S. Glenn **http://jci.me/90853**

Myeloid-related protein-14 regulates deep vein thrombosis

Yunmei Wang, Huiyun Gao, Chase W. Kessinger, Alvin Schmaier, Farouc A. Jaffer, and Daniel I. Simon **http://jci.me/91356**

CXCL13-producing T_{FH} cells link immune suppression and adaptive memory in human breast cancer

Chunyan Gu-Trantien, Edoardo Migliori, Laurence Buisseret, Alexandre de Wind, Sylvain Brohée, Soizic Garaud, Grégory Noël, Vu Luan Dang Chi, Jean-Nicolas Lodewyckx, Céline Naveaux, Hugues Duvillier, Stanislas Goriely, Denis Larsimont, and Karen Willard-Gallo **http://jci.me/91487**

Molecular imaging of oxidized collagen quantifies pulmonary and hepatic fibrogenesis

Howard H. Chen, Philip A. Waghorn, Lan Wei, Luis F. Tapias, Daniel T. Schühle, Nicholas J. Rotile, Chloe M. Jones, Richard J. Looby, Gaofeng Zhao, Justin M. Elliott, Clemens K. Probst, Mari Mino-Kenudson, Gregory Y. Lauwers, Andrew M. Tager, Kenneth K. Tanabe, Michael Lanuti, Bryan C. Fuchs, and Peter Caravan **http://jci.me/91506**

Delayed decompression exacerbates ischemia-reperfusion injury in cervical compressive myelopathy

Pia M. Vidal, Spyridon K. Karadimas, Antigona Ulndreaj, Alex M. Laliberte, Lindsay Tetreault, Stefania Forner, Jian Wang, Warren D. Foltz, and Michael G. Fehlings **http://jci.me/92512**

Tristetraprolin expression by keratinocytes controls local and systemic inflammation

Mathieu Andrianne, Assiya Assabban, Caroline La, Denis Mogilenko, Delphine Staumont Salle, Sébastien Fleury, Gilles Doumont, Gaëtan Van Simaeys, Sergei A. Nedospasov, Perry J. Blackshear, David Dombrowicz, Stanislas Goriely, and Laurye Van Maele **http://jci.me/92979**

Integrin-Kindlin3 requirements for microglial motility in vivo are distinct from those for macrophages

Julia Meller, Zhihong Chen, Tejasvi Dudiki, Rebecca M. Cull, Rakhilya Murtazina, Saswat K. Bal, Elzbieta Pluskota, Samantha Stefl, Edward F. Plow, Bruce D. Trapp, and Tatiana V. Byzova **http://jci.me/93002**

Identification and characterization of a supraclavicular brown adipose tissue in mice

Qianxing Mo, Jordan Salley, Tony Roshan, Lisa A. Baer, Francis J. May, Eric J. Jaehnig, Adam C. Lehnig, Xin Guo, Qiang Tong, Alli M. Nuotio-Antar, Farnaz Shamsi, Yu-Hua Tseng, Kristin I. Stanford, and Miao-Hsueh Chen **http://jci.me/93166**

Optimized multiplex immunofluorescence single-cell analysis reveals tuft cell heterogeneity ▶ p. 12

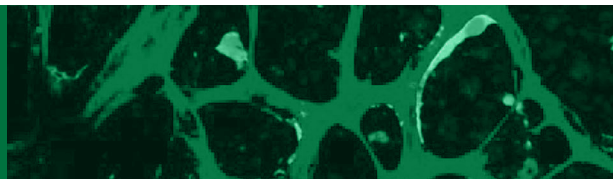
Eliot T. McKinley, Yunxia Sui, Yousef Al-Kofahi, Bryan A. Millis, Matthew J. Tyska, Joseph T. Roland, Alberto Santamaria-Pang, Christina L. Ohland, Christian Jobin, Jeffrey L. Franklin, Ken S. Lau, Michael J. Gerdes, and Robert J. Coffey **http://jci.me/93487**

Epithelial Gpr116 regulates pulmonary alveolar homeostasis via $G_{q/11}$ signaling

Kari Brown, Alyssa Filuta, Marie-Gabrielle Ludwig, Klaus Seuwen, Julian Jaros, Solange Vidal, Kavisha Arora, Anjaparavanda P. Naren, Kathirvel Kandasamy, Kaushik Parthasarathi, Stefan Offermanns, Robert J. Mason, William E. Miller, Jeffrey S. Whitsett, and James P. Bridges **http://jci.me/93700**

Network analysis of the genomic basis of the placebo effect ▶ p. 12

Rui-Sheng Wang, Kathryn T. Hall, Franco Giulianini, Dani Passow, Ted J. Kaptchuk, and Joseph Loscalzo **http://jci.me/93911**



Macrophage infiltration and genetic landscape of undifferentiated uterine sarcomas

Joanna Przybyl, Magdalena Kowalewska, Anna Quattrone, Barbara Dewaele, Vanessa Vanspauwen, Sushama Varma, Sujay Vennam, Aaron M. Newman, Michal Swierniak, Elwira Bakuła-Zalewska, Janusz A. Siedlecki, Maruisz Bidzinski, Jan Cools, Matt van de Rijn, and Maria Debiec-Rychter http://jci.me/94033

CD4+ T lymphocytes produce adiponectin in response to transplants ▶ p. 13

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A 3D microfluidic model for preclinical evaluation of TCR-engineered T cells against solid tumors

Andrea Pavesi, Anthony T. Tan, Sarene Koh, Adeline Chia, Marta Colombo, Emanuele Antonecchia, Carlo Miccolis, Erica Ceccarello, Giulia Adriani, Manuela T. Raimondi, Roger D. Kamm, and Antonio Bertoletti http://jci.me/89762

Dnmt3a-mediated inhibition of Wnt in cardiac progenitor cells improves differentiation and remote remodeling after infarction

Aurelia De Pauw, Emilie Andre, Belaid Sekkali, Caroline Bouzin, Hrag Esfahani, Nicolas Barbier, Axelle Loriot, Charles De Smet, Laetitia Vanhoutte, Stéphane Moniotte, Bernhard Gerber, Vittoria di Mauro, Daniele Catalucci, Olivier Feron, Denise Hilfiker-Kleiner, and Jean-Luc Balligand http://jci.me/91810

An activated Th17-prone T cell subset involved in chronic graft-versus-host disease sensitive to pharmacological inhibition

Edouard Forcade, Katelyn Paz, Ryan Flynn, Brad Griesenauer, Tohti Amet, Wei Li, Liangyi Liu, Giorgos Bakoyannis, Di Jiang, Hong Wei Chu, Mercedes Lobera, Jianfei Yang, David S. Wilkes, Jing Du, Kate Gartlan, Geoffrey R. Hill, Kelli P.A. MacDonald, Eduardo L. Espada, Patrick Blanco, Jonathan S. Serody, John Koreth, Corey S. Cutler, Joseph H. Antin, Robert J. Soiffer, Jerome Ritz, Sophie Paczesny, and Bruce R. Blazar http://jci.me/92111

α-Synuclein in gut endocrine cells and its implications for Parkinson's disease ▶ p. 11

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NELL-1 induces Sca-1+ mesenchymal progenitor cell expansion in models of bone maintenance and repair

Aaron W. James, Jia Shen, Rebecca Tsuei, Alan Nguyen, Kevork Khadarian, Carolyn A. Meyers, Hsin Chuan Pan, Weiming Li, Jin H. Kwak, Greg Asatrian, Cymbeline T. Culiat, Min Lee, Kang Ting, Xinli Zhang, and Chia Soo http://jci.me/92573

Genomic landscape and evolution of metastatic chromophobe renal cell carcinoma

Jozefina Casuscelli, Nils Weinhold, Gunes Gundem, Lu Wang, Emily C. Zabor, Esther Drill, Patricia I. Wang, Gouri J. Nanjangud, Almedina Redzematovic, Amrita M. Nargund, Brandon J. Manley, Maria E. Arcila, Nicholas M. Donin, John C. Cheville, R. Houston Thompson, Allan J. Pantuck, Paul Russo, Emily H. Cheng, William Lee, Satish K. Tickoo, Irina Ostrovnaya, Chad J. Creighton, Elli Papaemmanuil, Venkatraman E. Seshan, A. Ari Hakimi, and James J. Hsieh
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In vivo kinetics and novel nonradioactive imaging of rapidly proliferating cells in graft-versus-host disease

Nataliya P. Buxbaum, Donald E. Farthing, Natella Maglakelidze, Martin Lizak, Hellmut Merkle, Andrea C. Carpenter, Brittany U. Oliver, Veena Kapoor, Ehydel Castro, Gregory A. Swan, Liliane M. dos Santos, Nicolas J. Bouladoux, Catherine V. Bare, Francis A. Flomerfelt, Michael A. Eckhaus, William G. Telford, Yasmine Belkaid, Remy J. Bosselut, and Ronald E. Gress http://jci.me/92851

Delineating antibody recognition against Zika virus during natural infection

Lei Yu, Ruoke Wang, Fei Gao, Min Li, Jianying Liu, Jian Wang, Wenxin Hong, Lingzhai Zhao, Yingfen Wen, Chibiao Yin, Hua Wang, Qi Zhang, Yangyang Li, Panpan Zhou, Rudian Zhang, Yang Liu, Xiaoping Tang, Yongjun Guan, Chengfeng Qin, Ling Chen, Xuanling Shi, Xia Jin, Gong Cheng, Fuchun Zhang, and Linqi Zhang
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Robust memory responses against influenza vaccination in pemphigus patients previously treated with rituximab

Alice Cho, Bridget Bradley, Robert Kauffman, Lalita Priyamvada, Yevgeniy Kovalenkov, Ron Feldman, and Jens Wrammert http://jci.me/93222

Mitochondrial dysregulation and glycolytic insufficiency functionally impair CD8 T cells infiltrating human renal cell carcinoma

Peter J. Siska, Kathryn E. Beckermann, Frank M. Mason, Gabriela Andrejeva, Allison R. Greenplate, Adam B. Sendor, Yun-Chen J. Chiang, Armando L. Corona, Lelisa F. Gemta, Benjamin G. Vincent, Richard C. Wang, Bumki Kim, Jiyong Hong, Chiu-Ian Chen, Timothy N. Bullock, Jonathan M. Irish, W. Kimryn Rathmell, and Jeffrey C. Rathmell **http://jci.me/93411**

DNA methyltransferase 3b regulates articular cartilage homeostasis by altering metabolism

Jie Shen, Cuicui Wang, Daofeng Li, Taotao Xu, Jason Myers, John M. Ashton, Ting Wang, Michael J. Zuscik, Audrey McAlinden, and Regis J. O'Keefe **http://jci.me/93612**

Human vaccination against *Plasmodium vivax* Duffy-binding protein induces strain-transcending antibodies

Ruth O. Payne, Sarah E. Silk, Sean C. Elias, Kathryn H. Milne, Thomas A. Rawlinson, David Llewellyn, A. Rushdi Shakri, Jing Jin, Geneviève M. Labbé, Nick J. Edwards, Ian D. Poulton, Rachel Roberts, Ryan Farid, Thomas Jørgensen, Daniel G.W. Alanine, Simone C. de Cassan, Matthew K. Higgins, Thomas D. Otto, James S. McCarthy, Willem A. de Jongh, Alfredo Nicosia, Sarah Moyle, Adrian V.S. Hill, Eleanor Berrie, Chetan E. Chitnis, Alison M. Lawrie, and Simon J. Draper **http://jci.me/93683**

A single dose of cannabidiol reduces blood pressure in healthy volunteers in a randomized crossover study

Khalid A. Jadoon, Garry D. Tan, and Saoirse E. O'Sullivan **http://jci.me/93760**

Apelin modulates pathological remodeling of lymphatic endothelium after myocardial infarction

Florence Tatin, Edith Renaud-Gabardos, Anne-Claire Godet, Fransky Hantelys, Francoise Pujol, Florent Morfoisse, Denis Calise, Fanny Viars, Philippe Valet, Bernard Masri, Anne-Catherine Prats, and Barbara Garmy-Susini **http://jci.me/93887**

Neuropeptide Y expression marks partially differentiated β cells in mice and humans

Pope Rodnoi, Mohan Rajkumar, Abu Saleh Md Moin, Senta K. Georgia, Alexandra E. Butler, and Sangeeta Dhawan **http://jci.me/94005**

Assessing rejection-related disease in kidney transplant biopsies based on archetypal analysis of molecular phenotypes

Jeff Reeve, Georg A. Böhmig, Farsad Eskandary, Gunilla Einecke, Carmen Lefaucheur, Alexandre Loupy, Philip F. Halloran, and the MMDx-Kidney study group **http://jci.me/94197**

Type I interferons suppress viral replication but contribute to T cell depletion and dysfunction during chronic HIV-1 infection ▶ p. 11

Liang Cheng, Haisheng Yu, Guangming Li, Feng Li, Jianping Ma, Jingyun Li, Liqun Chi, Liguo Zhang, and Lishan Su **http://jci.me/94366**

PERSPECTIVE

Globalization and changing trends of biomedical research output

Marisa L. Conte, Jing Liu, Santiago Schnell, and M. Bishr Omary **http://jci.me/95206**

REVIEW

Immunity against fungi

Michail D. Lionakis, Iliyan D. Iliev, and Tobias M. Hohl **http://jci.me/93156**

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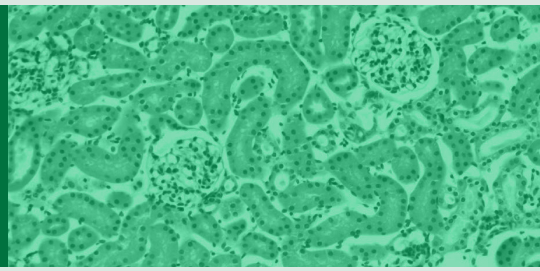

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