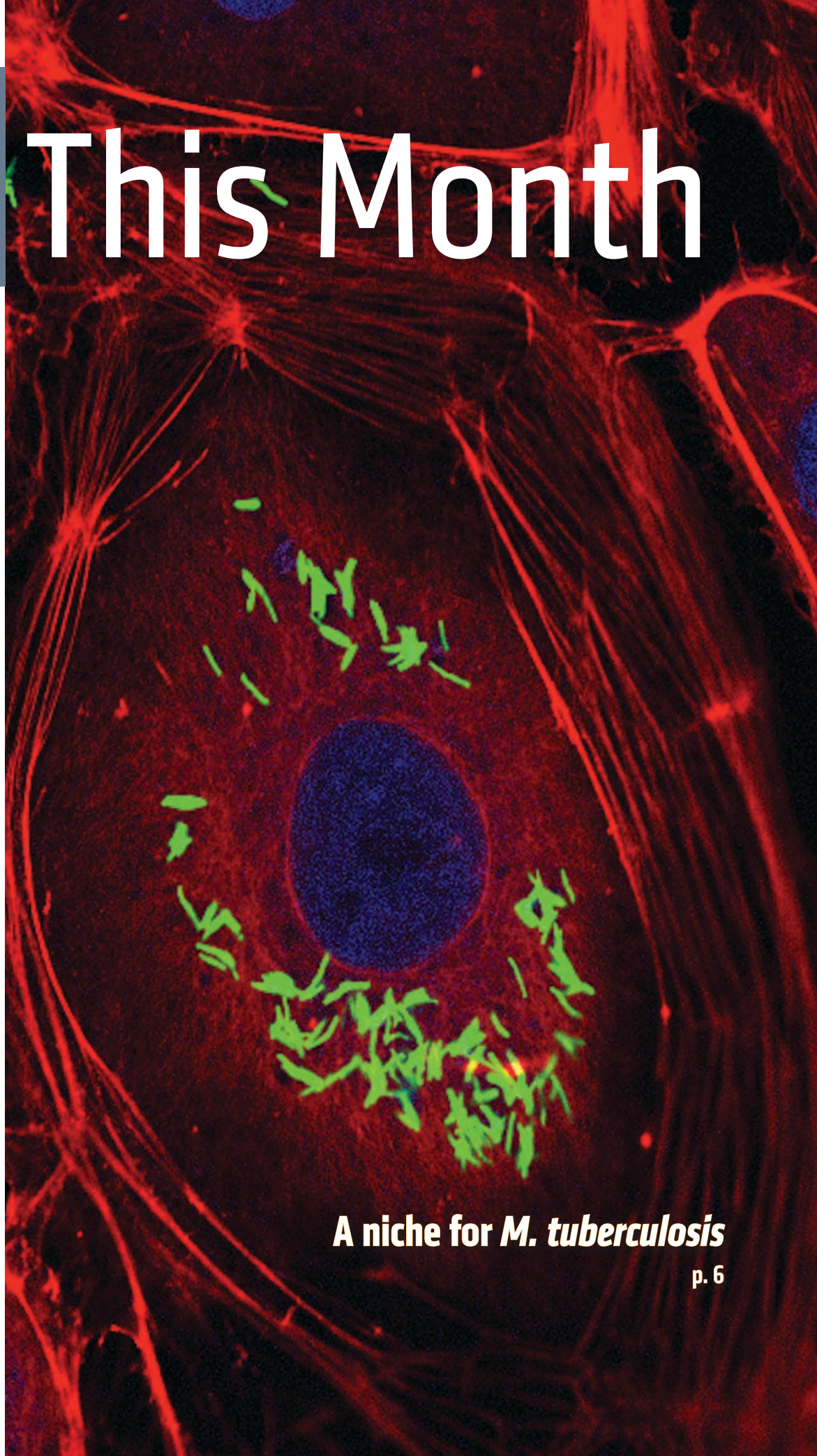
JCI This Month

March 2016

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



A niche for *M. tuberculosis*
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JCI This Month

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Featured Editor

The JCI's Editorial Board is composed of peer scientists at Duke University Medical Center, the University of North Carolina, Duke-NUS, and the Sanford-Burnham Medical Research Institute. Editorial Board members review and oversee peer review of each manuscript that is submitted to the JCI, and the board meets weekly to discuss the manuscripts undergoing review.

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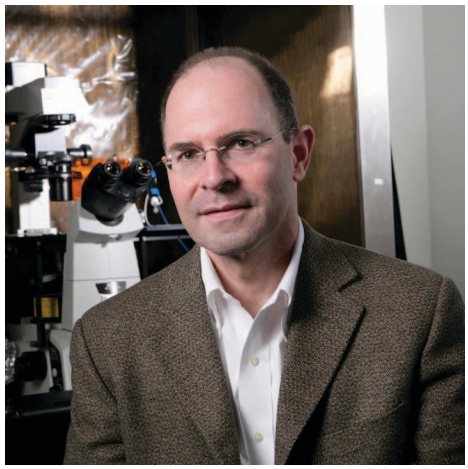

Geoffrey Pitt, MD, PhD, Associate Editor, is a Professor of Medicine in the Division of Cardiology at Duke University and the Director of the Ion Channel Research Unit. Dr. Pitt was elected to the American Society for Clinical Investigation in 2007 and the Association of American Physicians in 2013. Dr. Pitt's research explores how ion channels function in physiology and how ion channel dysfunction leads to disease. Current areas of interest in the Pitt laboratory include mechanisms of channel function and dysfunction in inherited cardiac channelopathies, neuropsychiatric disorders, synaptic plasticity, and developmental disorders.

Publication highlights

Ramachandran KV, Hennessey JA, Barnett AS, Yin X, Stadt HA, Foster E, Shah RA, Yazawa M, Dolmetsch RE, Kirby ML, Pitt GS. Calcium influx through L-type CaV1.2 Ca^{2+} channels regulates mandibular development. *J Clin Invest*. 2013;123(4):1638–1646.

Wang C, Hennessey JA, Kirkton RD, Wang C, Graham V, Puranam RS, Rosenberg PB, Bursac N, Pitt GS. Fibroblast growth factor homologous factor 13 regulates Na^{+} channels and conduction velocity in murine hearts. *Circ Res*. 2011;109(7):775–782.

Yan H, Pablo JL, Wang C, Pitt GS. FGF14 modulates resurgent sodium current in mouse cerebellar Purkinje neurons. *Elife*. 2014;3:e04193.

Wang C, Chung BC, Yan H, Wang HG, Lee SY, Pitt GS. Structural analyses of Ca^{2+}/CaM interaction with NaV channel C-termini reveal mechanisms of calcium-dependent regulation. *Nat Commun*. 2014;5:4896.

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For JCI Insight:
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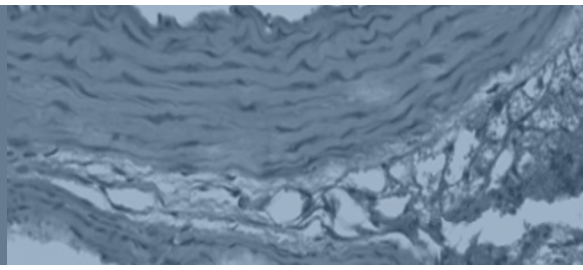
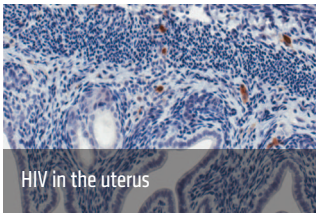
Research articles in the current issue of the JCI




HIV in the uterus

AIDS/HIV

ART influences HIV persistence in the female reproductive tract and cervicovaginal secretions

Rikke Olesen, Michael D. Swanson, Martina Kovarova, Tomonori Nochi, Morgan Chateau, Jenna B. Honeycutt, Julie M. Long, Paul W. Denton, Michael G. Hudgens, Amy Richardson, Martin Tolstrup, Lars Østergaard, Angela Wahl, and J. Victor Garcia **http://jci.me/64212**

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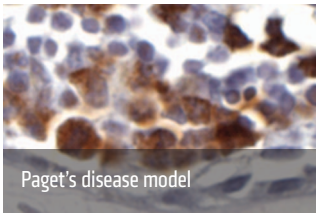
Paget's disease model

Bone biology

Measles virus nucleocapsid protein increases osteoblast differentiation in Paget's disease

Jumpei Teramachi, Yuki Nagata, Khalid Mohammad, Yuji Inagaki, Yasuhisa Ohata, Theresa Guise, Laëtitia Michou, Jacques P. Brown, Jolene J. Windle, Noriyoshi Kurihara, and G. David Roodman
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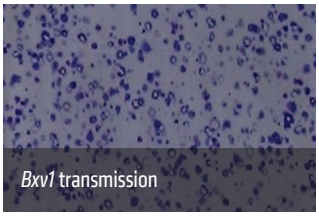
Cell biology


Bxv1 transmission

Xenotropic retrovirus *Bxv1* in human pancreatic β cell lines

Jeannette S. Kirkegaard, Philippe Ravassard, Signe Ingvarsen, Marc Diedisheim, Emilie Bricout-Neveu, Mads Grønborg, Thomas Frogne, Raphael Scharfmann, Ole D. Madsen, Claude Rescan, and Olivier Albagli
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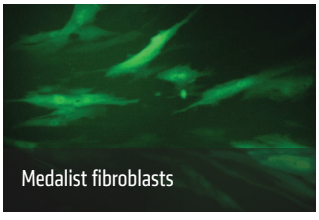
Endocrinology


Medalist fibroblasts

PKCδ inhibition normalizes the wound-healing capacity of diabetic human fibroblasts

Mogher Khamaisi, Sayaka Katagiri, Hillary Keenan, Kyoungmin Park, Yasutaka Maeda, Qian Li, Weier Qi, Thomas Thomou, Danielle Eschuk, Ana Tellechea, Aris Veves, Chenyu Huang, Dennis Paul Orgill, Amy Wagers, and George L. King
http://jci.me/82788

Gonadal steroid–dependent effects on bone turnover and bone mineral density in men

Joel S. Finkelstein, Hang Lee, Benjamin Z. Leder, Sherri-Ann M. Burnett-Bowie, David W. Goldstein, Christopher W. Hahn, Sarah C. Hirsch, Alex Linker, Nicholas Perros, Andrew B. Servais, Alexander P. Taylor, Matthew L. Webb, Jonathan M. Youngner, and Elaine W. Yu
http://jci.me/84137

With related Commentary by Thomas J. Weber

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Lineage-affiliated transcription factors bind the *Gata3 Tce1* enhancer to mediate lineage-specific programs

Sakie Ohmura, Seiya Mizuno, Hisashi Oishi, Chia-Jui Ku, Mary Hermann, Tomonori Hosoya, Satoru Takahashi, and James Douglas Engel
http://jci.me/83894

Mutation in human selenocysteine transfer RNA selectively disrupts selenoprotein synthesis

Erik Schoenmakers, Bradley Carlson, Maura Agostini, Carla Moran, Odelia Rajanayagam, Elena Bochukova, Ryuta Tobe, Rachel Peat, Evelien Gevers, Francesco Muntoni, Pascale Guicheney, Nadia Schoenmakers, Sadaf Farooqi, Greta Lyons, Dolph Hatfield, and Krishna Chatterjee
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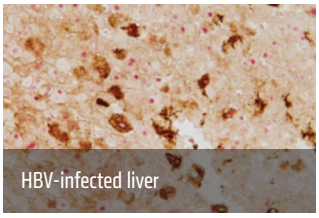
Hepatology


HBV-infected liver

In situ analysis of intrahepatic virological events in chronic hepatitis B virus infection

Xiaonan Zhang, Wei Lu, Ye Zheng, Weixia Wang, Lu Bai, Liang Chen, Yanling Feng, Zhanqing Zhang, and Zhenghong Yuan http://jci.me/83339

With related Commentary by Peter A. Revill and Stephen A. Locarnini

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Hepatocyte mitochondrial DNA drives nonalcoholic steatohepatitis by activation of TLR9

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T regulatory cell chemokine production mediates pathogenic T cell attraction and suppression

Scott J. Patterson, Anne M. Pesenacker, Adele Y. Wang, Jana Gillies, Majid Mojibian, Kim Morishita, Rusung Tan, Timothy J. Kieffer, C. Bruce Verchere, Constadina Panagiotopoulos, and Megan K. Levings
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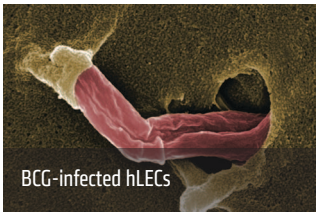
Neonatal thymectomy reveals differentiation and plasticity within human naive T cells

Theo van den Broek, Eveline M. Delemarre, Willemijn J.M. Janssen, Rutger A.J. Nievelstein, Jasper C. Broen, Kiki Tesselaar, Jose A.M. Borghans, Edward E.S. Nieuwenhuis, Berent J. Prakken, Michal Mokry, Nicolaas J.G. Jansen, and Femke van Wijk
http://jci.me/84997


BCG-infected hLECs

Infectious disease

Lymphatic endothelial cells are a replicative niche for *Mycobacterium tuberculosis*

Thomas R. Lerner, Cristiane de Souza Carvalho-Wodarz, Urska Repnik, Matthew R.G. Russell, Sophie Borel, Collin R. Diedrich, Manfred Rohde, Helen Wainwright, Lucy M. Collinson, Robert J. Wilkinson, Gareth Griffiths, and Maximiliano G. Gutierrez http://jci.me/83379

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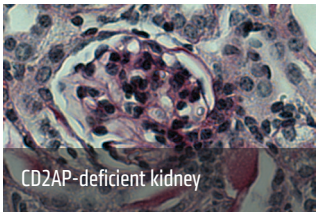
Nephrology


CD2AP-deficient kidney

A role for genetic susceptibility in sporadic focal segmental glomerulosclerosis

Haiyang Yu, Mykyta Artomov, Sebastian Brähler, M. Christine Stander, Ghaidan Shamsan, Matthew G. Sampson, J. Michael White, Matthias Kretzler, Jeffrey H. Miner, Sanjay Jain, Cheryl A. Winkler, Robi D. Mitra, Jeffrey B. Kopp, Mark J. Daly, and Andrey S. Shaw **http://jci.me/82592**

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FGF23 signaling impairs neutrophil recruitment and host defense during CKD

Jan Rossaint, Jessica Oehmichen, Hugo Van Aken, Stefan Reuter, Hernann J. Pavenstädt, Melanie Meersch, Mark Unruh, and Alexander Zarbock
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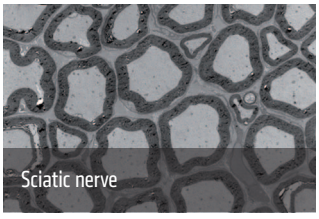
Neuroscience

Temporal integration of light flashes by the human circadian system

Raymond P. Najjar and Jamie M. Zeitzer **http://jci.me/82306**


Sciatic nerve

Blocking mitochondrial calcium release in Schwann cells prevents demyelinating neuropathies

Sergio Gonzalez, Jade Berthelot, Jennifer Jiner, Claire Perrin-Tricaud, Ruani Fernando, Roman Chrast, Guy Lenaers, and Nicolas Tricaud
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Bin Zhang, Ling Li, Yinwei Ho, Min Li, Guido Marcucci, Wei Tong, and Ravi Bhatia **http://jci.me/79196**

Chemokine receptor patterns in lymphocytes mirror metastatic spreading in melanoma

Nicolas Jacquelot, David P. Enot, Caroline Flament, Nadège Vimond, Carolin Blattner, Jonathan M. Pitt, Takahiro Yamazaki, María Paula Roberti, Romain Daillère, Marie Vétizou, Vichnou Poirier-Colame, Michaëla Semeraro, Anne Caignard, Craig L. Slingluff Jr., Federica Sallusto, Sylvie Rusakiewicz, Benjamin Weide, Aurélien Marabelle, Holbrook Kohrt, Stéphane Dalle, Andréa Cavalcanti, Guido Kroemer, Anna Maria Di Giacomo, Michele Maio, Phillip Wong, Jianda Yuan, Jedd Wolchok, Viktor Umansky, Alexander Eggermont, and Laurence Zitvogel
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MLL-AF9– and HOXA9-mediated acute myeloid leukemia stem cell self-renewal requires JMJD1C

Nan Zhu, Mo Chen, Rowena Eng, Joshua DeJong, Amit U. Sinha, Noushin F. Rahnamay, Richard Koche, Fatima Al-Shahrour, Janna C. Minehart, Chun-Wei Chen, Aniruddha J. Deshpande, Haiming Xu, S. Haihua Chu, Benjamin L. Ebert, Robert G. Roeder, and Scott A. Armstrong
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Targeting human melanoma neoantigens by T cell receptor gene therapy

Matthias Leisegang, Thomas Kammertoens, Wolfgang Uckert, and Thomas Blankenstein http://jci.me/83465

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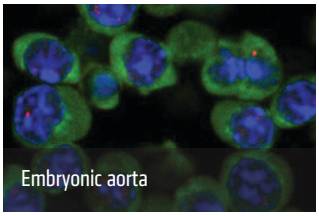

Histone demethylase KDM2B regulates lineage commitment in normal and malignant hematopoiesis

Jaclyn Andricovich, Yan Kai, Weiqun Peng, Adlen Foudi, and Alexandros Tzatsos
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Genomic and transcriptomic hallmarks of poorly differentiated and anaplastic thyroid cancers

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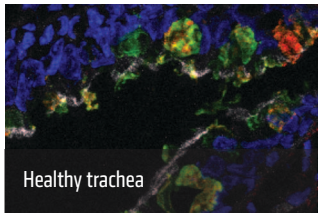

Pulmonology

Acidic pH increases airway surface liquid viscosity in cystic fibrosis

Xiao Xiao Tang, Lynda S. Ostedgaard, Mark J. Hoegger, Thomas O. Moninger, Philip H. Karp, James D. McMenimen, Biswa Choudhury, Ajit Varki, David A. Stoltz, and Michael J. Welsh
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Vascular biology

FOXE3 mutations predispose to thoracic aortic aneurysms and dissections

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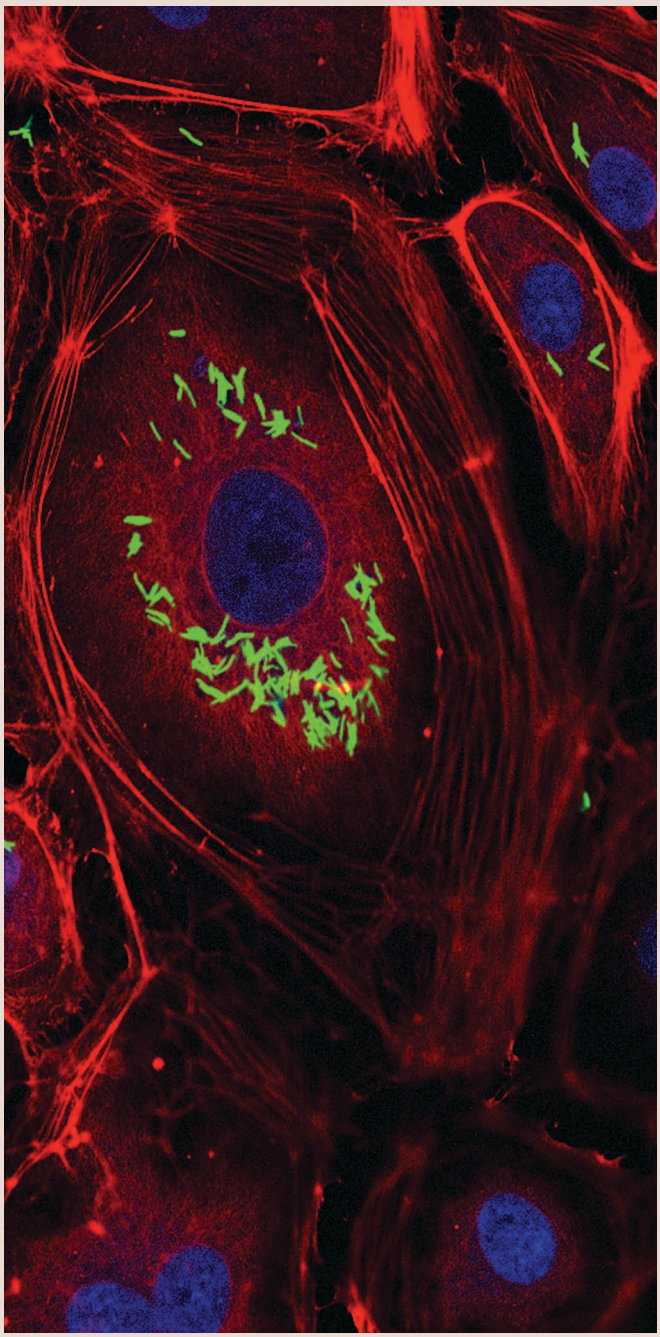
Editor's picks

Lymphatic endothelial cells are a locus for extrapulmonary tuberculosis infection

***Mycobacterium tuberculosis* infection** most commonly occurs in the lungs. In some cases, tissues outside the lung, including the lymph nodes, can also be infected, particularly in immunocompromised patients. In this month's issue of the *JCI*, a research team led by Maximiliano Gutierrez reports that lymphatic endothelial cells within the lymphatic vascular system harbor *M. tuberculosis* and serve as a site for bacterial replication. In human lymph node tissue from patients diagnosed with tuberculosis, the authors detected *M. tuberculosis* within lymphatic endothelial cells. They subsequently showed, in primary human lymph node–derived endothelial cells cultured in vitro, that *M. tuberculosis* localizes primarily within the cytosol and, to a lesser extent, within membrane-bound compartments, such as phagosomes, lysosomes, and autophagosomes. Moreover, they showed that *M. tuberculosis* was able to grow within autophagosomes. Stimulation of lymphatic endothelial cells with IFN-γ, a cytokine that has been implicated in control of *M. tuberculosis*, restricted bacterial replication in a manner dependent on the presence of the *M. tuberculosis* RD1 virulence locus. The researchers found that IFN-γ stimulates nitric oxide production in lymphatic endothelial cells and that the nitric oxide synthase inhibitor L-NMMA blocked the inhibitory effect of IFN-γ on *M. tuberculosis* growth. Together, these findings provide new evidence that lymphatic endothelial cells can serve as a replicative niche for *M. tuberculosis* and suggest a mechanism for sustained infection in the lymphatic system. The accompanying image shows human primary lymphatic endothelial cells (actin, red; nuclei, blue) infected with mycobacteria expressing EGFP (green).



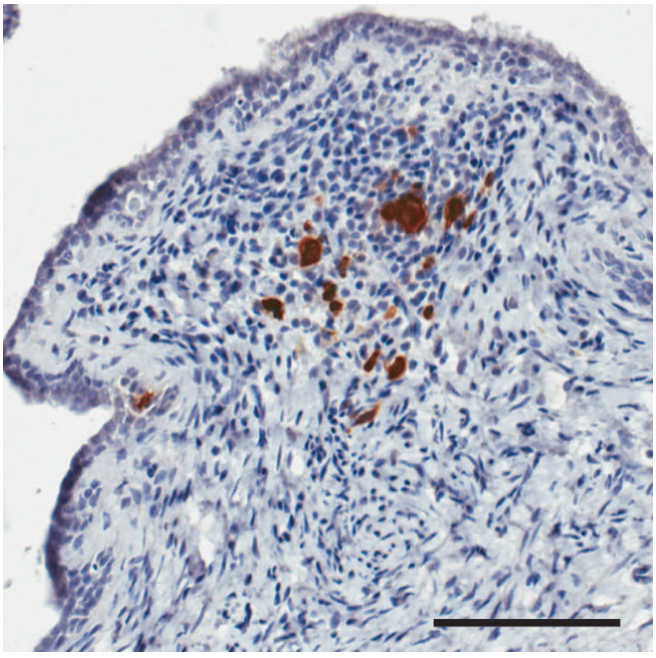
Lymphatic endothelial cells are a replicative niche for *Mycobacterium tuberculosis*

Thomas R. Lerner, Cristiane de Souza Carvalho-Wodarz, Urska Repnik, Matthew R.G. Russell, Sophie Borel, Collin R. Diedrich, Manfred Rohde, Helen Wainwright, Lucy M. Collinson, Robert J. Wilkinson, Gareth Griffiths, and Maximiliano G. Gutierrez **http://jci.me/83379**

AIDS/HIV

Antiretroviral therapy reduces HIV in the female reproductive tract

A recent HIV prevention clinical trial demonstrated 93% protection against secondary heterosexual transmission when infected partners received early antiretroviral therapy (ART). Rikke Olesen and colleagues tested the hypothesis that ART reduces genital cell–free or genital cell–associated HIV to levels that are too low to support HIV transmission. Using the humanized BM/liver/thymus (BLT) mouse model, they demonstrated that humanized $CD4^+$ T cells were present throughout the female reproductive tract (FRT) and that these cells were shed into cervicovaginal secretions (CVS). HIV infection increased the number of $CD4^+$ and $CD8^+$ T cells in the CVS, and virus was present throughout the FRT (see the accompanying image) and in CVS. ART strongly suppressed CVS viral load; however, HIV-RNA^+ cells were present in both the FRT and the CVS, though these cells did not transmit HIV in an in vitro coculture assay.



ART influences HIV persistence in the female reproductive tract and cervicovaginal secretions

Rikke Olesen, Michael D. Swanson, Martina Kovarova, Tomonori Nochi, Morgan Chateau, Jenna B. Honeycutt, Julie M. Long, Paul W. Denton, Michael G. Hudgens, Amy Richardson, Martin Tolstrup, Lars Østergaard, Angela Wahl, and J. Victor Garcia

http://jci.me/64212

IMMUNOLOGY

Tregs produce chemokines to attract and suppress adaptive immune cells

Regulatory T cells (Tregs) prevent inappropriate responses to self and nonharmful foreign antigens, and modulation of Treg activity is a potential strategy to treat immune-mediated disease. Scott Patterson, Anne Pesenacker, and colleagues demonstrate that Tregs produce the chemokines CCL3 and CCL4 to attract $CD4^+$ and $CD8^+$ T cells via the receptor CCR5, drawing these cell populations close, possibly increasing proximity-dependent regulation of their activity. WT and *Ccl3*-deficient Tregs were comparable in their activation phenotypes and ability to suppress T cell proliferation in vitro, while *Ccl3*-deficient Tregs were unable to attract $CD4^+$ and $CD8^+$ T cells. Using murine models of multiple sclerosis and islet allograft rejection, Patterson, Pesenacker, and colleagues demonstrate that transplantation of *Ccl3*-deficient Tregs did not lead to the reductions in disease severity or progression that were seen with transplantation of WT Tregs. Finally, they observe that Tregs from patients with established type 1 diabetes had decreased CCL3 and CCL4 production compared with Tregs from healthy individuals.

T regulatory cell chemokine production mediates pathogenic T cell attraction and suppression

Scott J. Patterson, Anne M. Pesenacker, Adele Y. Wang, Jana Gillies, Majid Mojibian, Kim Morishita, Rusung Tan, Timothy J. Kieffer, C. Bruce Verchere, Constadina Panagiotopoulos, and Megan K. Levings

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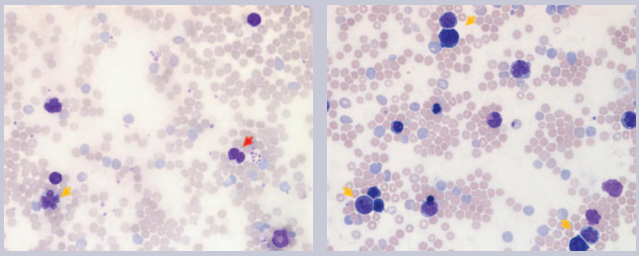
ONCOLOGY

Lysine-specific demethylase 2B regulates hematopoietic lineage commitment



Transcriptional and epigenetic networks regulate hematopoietic lineage specification, and these networks are frequently dysregulated in hematopoietic malignancies. Jaclyn Andricovich and colleagues investigated the role of lysine-specific demethylase 2B (KDM2B) in lineage commitment by analyzing hematopoietic stem and progenitor cells (HSPCs) from mice that were engineered to conditionally ablate or overexpress KDM2B in the hematopoietic system. They found that KDM2B was required for embryonic development and definitive hematopoiesis. RNA sequencing revealed that KDM2B regulates developmental pathways by binding repressed and activated chromatin through interactions with polycomb and trithorax group complexes, respectively. Additionally, they demonstrate that KDM2B functions as either a tumor suppressor or an oncogene, depending on the cellular context. The accompanying image shows accelerated Kras-driven myeloid transformation in KDM2B-deficient peripheral blood.

Histone demethylase KDM2B regulates lineage commitment in normal and malignant hematopoiesis
Jaclyn Andricovich, Yan Kai, Weiqun Peng, Adlen Foudi, and Alexandros Tzatsos **http://jci.me/84014**

Chemokine receptor expression on lymphocytes influences melanoma spread

The abundance, trafficking, and characteristics of tumor-infiltrating lymphocytes (TILs) strongly influence the prognosis of human malignancies including metastatic melanoma (MMel). Lymphocyte trafficking into the tumor is largely determined by the expression of chemokine receptors on peripheral T cells (peripheral blood mononuclear cells [PBMCs]). Nicolas Jacquelot and colleagues analyzed PBMCs and TILs from MMel patients to determine whether chemokine receptor expression correlated with intratumoral accumulation, metastatic progression, or overall survival (OS). They found that T cell chemokine receptor expression was strongly correlated with MMel dissemination and that the expression of specific chemokine receptors was associated with metastases at different sites, such as the skin, lymph nodes, or lungs. Importantly, expression of CCR9 on naive $CD8^+$ peripheral T cells correlated with increased OS in patients, while inhibition of CCR9 signaling stimulated tumor progression in mice. Taken together, these results suggest that specific chemokine receptor expression patterns could help guide diagnostic and therapeutic approaches.

Chemokine receptor patterns in lymphocytes mirror metastatic spreading in melanoma
Nicolas Jacquelot, David P. Enot, Caroline Flament, Nadège Vimond, Carolin Blattner, Jonathan M. Pitt, Takahiro Yamazaki, María Paula Roberti, Romain Daillère, Marie Vétizou, Vichnou Poirier-Colame, Michaëla Semeraro, Anne Caignard, Craig L. Slingluff Jr., Federica Sallusto, Sylvie Rusakiewicz, Benjamin Weide, Aurélien Marabelle, Holbrook Kohrt, Stéphane Dalle, Andréa Cavalcanti, Guido Kroemer, Anna Maria Di Giacomo, Michele Maio, Phillip Wong, Jianda Yuan, Jedd Wolchok, Viktor Umansky, Alexander Eggermont, and Laurence Zitvogel
http://jci.me/80071

Neoantigen quality determines T cell receptor gene therapy effectiveness

Immunotherapy-induced melanoma regression is associated with increased frequencies of neoantigen-specific T cells; however, the fate and function of these cells are unclear. Matthias Leisegang and colleagues generated T cells expressing a transgenic T cell receptor (TCR) recognizing two different naturally occurring immunogenic mutations in the same position in cyclin-dependent kinase 4 (CDK4). Using a murine model of large, established tumors, they demonstrate that these T cells produced an effective antitumor response when the tumor expressed the $CDK4^{R24L}$ mutation, but failed when the tumor expressed the $CDK4^{R24C}$ mutation. These results suggest that neoantigen quality, which is not always measurable by in vitro assays, may underlie differences in patient responses to immunotherapy.

Targeting human melanoma neoantigens by T cell receptor gene therapy
Matthias Leisegang, Thomas Kammertoens, Wolfgang Uckert, and Thomas Blankenstein
http://jci.me/83465

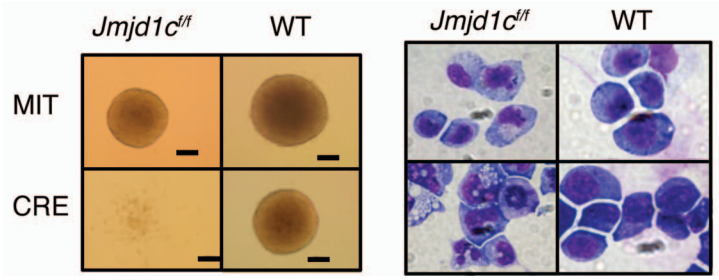
ONCOLOGY

Jumonji domain–containing protein JMJD1C regulates leukemia stem cell self-renewal

Both hematopoietic stem cells (HSCs) and leukemia stem cells (LSCs) are capable of self-renewal. Identification of mechanisms underlying LSC but not HSC self-renewal could be therapeutically exploited to reduce the toxicity of leukemia treatment. Nan Zhu and colleagues performed an in vivo shRNA screen and identified the jumonji domain–containing protein JMJD1C as a critical regulator of LSC self-renewal in MLL-AF9– and HOXA9-driven leukemias. Loss of JMJDC1 decreased LSC frequency (see the accompanying image), drove differentiation of leukemic cells, and prolonged survival, but caused only minor defects in HSC self-renewal and blood homeostasis. Zhu and colleagues show that JMJDC1 interacted with HOXA9 to modulate gene expression. These data demonstrate that JMJDC1 selectively modulates LSC self-renewal in MLL-AAF9– and HOXA9-driven leukemias.

MLL-AF9– and HOXA9-mediated acute myeloid leukemia stem cell self-renewal requires JMJD1C

Nan Zhu, Mo Chen, Rowena Eng, Joshua DeJong, Amit U. Sinha, Noushin F. Rahnamay, Richard Koche, Fatima Al-Shahrour, Janna C. Minehart, Chun-Wei Chen, Aniruddha J. Deshpande, Haiming Xu, S. Haihua Chu, Benjamin L. Ebert, Robert G. Roeder, and Scott A. Armstrong http://jci.me/82978



ENDOCRINOLOGY

Bone homeostasis in men is primarily regulated by estradiol

Severe gonadal steroid deficiency induces bone loss in adult men; however, the specific roles of androgens and estrogens in male bone homeostasis are unclear. Joel S. Finkelstein and colleagues conducted a clinical study in which healthy men were treated with the gonadotropin-releasing hormone agonist goserelin to induce severe gonadal steroid deficiency. The trial subjects also received either placebo testosterone or one of a range of doses of testosterone gel. Half the men also received the aromatase inhibitor anastrozole to inhibit the conversion of testosterone to estradiol. Decreasing doses of testosterone were inversely correlated with serum C-telopeptide, a marker of bone turnover. Moreover, anastrozole treatment increased bone turnover and decreased bone mineral density, indicating that estradiol is required to maintain bone homeostasis. In the accompanying Commentary, Thomas J. Weber discusses how this study reveals a dominant effect of estradiol in suppressing bone resorption.

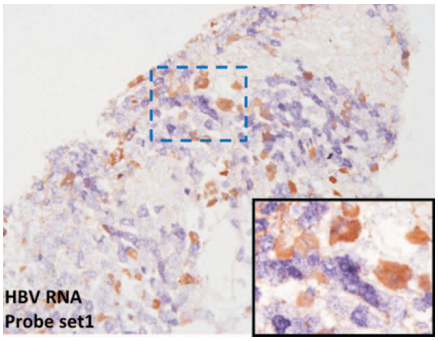
Gonadal steroid–dependent effects on bone turnover and bone mineral density in men

Joel S. Finkelstein, Hang Lee, Benjamin Z. Leder, Sherri-Ann M. Burnett-Bowie, David W. Goldstein, Christopher W. Hahn, Sarah C. Hirsch, Alex Linker, Nicholas Perros, Andrew B. Servais, Alexander P. Taylor, Matthew L. Webb, Jonathan M. Youngner, and Elaine W. Yu
http://jci.me/84137

▶ Related Commentary
Battle of the sex steroids in the male skeleton: and the winner is...
Thomas J. Weber
http://jci.me/85006

HEPATOLOGY

Mapping the intrahepatic distribution of hepatitis B virus



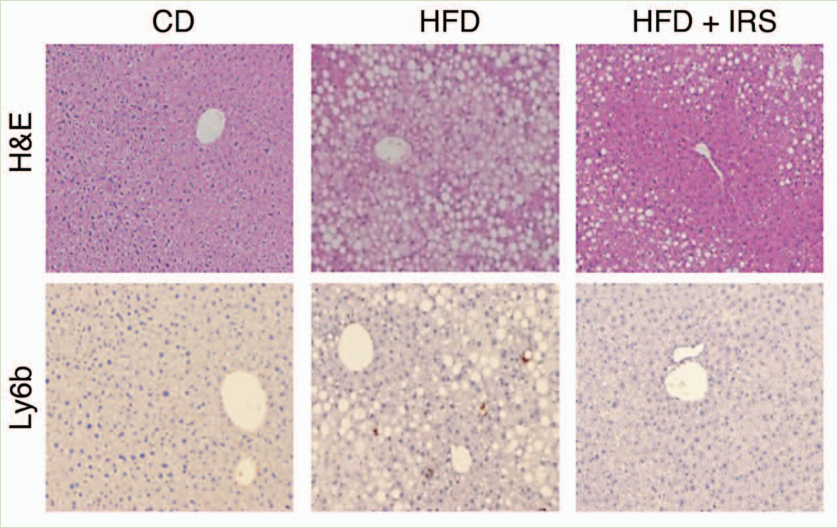
Persistent hepatitis B virus (HBV) infection is established by the formation of an intranuclear pool of covalently closed circular DNA (cccDNA). Xiaonan Zhang and colleagues developed an ISH assay to examine the intrahepatic distribution of HBV RNA, DNA, and cccDNA at the single-cell level in liver biopsies from patients with chronic HBV. ISH, in combination with immune-detection of major HBV antigens, showed that viral nucleic acids and antigens had a mosaic-like distribution and that the presence of HBV surface antigens and DNA was mutually exclusive (see the accompanying image). Serial biopsies from patients before and after 1 year of treatment with the reverse transcriptase inhibitor adefovir demonstrated the persistence of a nuclear reservoir of HBV DNA and depletion of cytoplasmic HBV DNA. In the accompanying Commentary, Stephen Locarnini and Peter Revill discuss how this study chronicles the HBV life cycle in vivo.

In situ analysis of intrahepatic virological events in chronic hepatitis B virus infection
Xiaonan Zhang, Wei Lu, Ye Zheng, Weixia Wang, Lu Bai, Liang Chen, Yanling Feng, Zhanqing Zhang, and Zhenghong Yuan
http://jci.me/83339

▶ Related Commentary
New perspectives on the hepatitis B virus life cycle in the human liver
Peter A. Revill and Stephen A. Locarnini
http://jci.me/86650

TLR9 is activated by hepatocyte mitochondrial DNA in nonalcoholic steatohepatitis

Nonalcoholic steatohepatitis (NASH) is a progressive liver disease that can lead to cirrhosis, cancer, and death, but there are currently no approved treatments. Animal models of NASH require TLR9 signaling, but it is unclear how TLR9 contributes to disease pathogenesis. Irma Garcia-Martinez and colleagues demonstrated that plasma from mice and patients with NASH contained high levels of mitochondrial DNA (mtDNA), which activates TLR9. Notably, the majority of the mtDNA was contained in hepatocyte-derived microparticles (MPs), and MP-depleted plasma had a decreased capacity to activate TLR9. Moreover, deletion of *Tlr9* in lysozyme-expressing cells or pharmacological inhibition of TLR9 blocked the development of NASH in mice fed a high-fat diet (see the accompanying image). These data demonstrate that NASH-associated metabolites contribute to disease pathogenesis via TLR9.



Hepatocyte mitochondrial DNA drives nonalcoholic steatohepatitis by activation of TLR9
Irma Garcia-Martinez, Nicola Santoro, Yonglin Chen, Rafaz Hoque, Xinshou Ouyang, Sonia Caprio, Mark J. Shlomchik, Robert Lee Coffman, Albert Candia, and Wajahat Zafar Mehal
http://jci.me/83885

NEPHROLOGY

Identifying the genetic underpinnings of sporadic focal segmental glomerulosclerosis

Focal segmental glomerulosclerosis (FSGS) is a syndrome in which kidney podocyte dysfunction causes glomerular scarring, leading to chronic kidney disease (CKD). Highly penetrant disease genes have been identified in a small fraction of patients with a family history of FSGS. Haiyang Yu, Mykyta Artomov, Sebastian Brähler, and colleagues performed high-throughput sequencing for 214 FSGS patients of Northern European ancestry, focusing on 2,500 genes that are highly or specifically expressed in podocytes to identify new FSGS disease–susceptibility genes. In addition to the 20 known genetic variants associated with FSGS, Yu, Artomov, Brähler, and colleagues identified 9 new candidate susceptibility genes, 3 of which (*KANK1*, *WNK4*, and *ARHGEF17*) were validated in a murine model based on shRNA targeting of candidate genes in an FSGS-susceptible embryonic stem cell line. These findings support a broader role for genetic susceptibility to FSGS than was previously appreciated.

A role for genetic susceptibility in sporadic focal segmental glomerulosclerosis

Haiyang Yu, Mykyta Artomov, Sebastian Brähler, M. Christine Stander, Ghaidan Shamsan, Matthew G. Sampson, J. Michael White, Matthias Kretzler, Jeffrey H. Miner, Sanjay Jain, Cheryl A. Winkler, Robi D. Mitra, Jeffrey B. Kopp, Mark J. Daly, and Andrey S. Shaw **http://jci.me/82592**

Chronic kidney disease–associated FGF23 elevation impairs host defense

Chronic kidney disease (CKD) is associated with impaired host immune defense and an increased susceptibility to infection; however, the mechanisms underlying this impairment are not clear. Jan Rossaint and colleagues report that elevated FGF23 levels in patients and mice with CKD inhibit leukocyte recruitment to inflamed tissues. Neutralization of FGF23 restored neutrophil recruitment and host defense in mice with CKD after induction of pneumonia. Mechanistically, Rossaint and colleagues demonstrated that FGF23 blocks slow rolling, arrest, and transendothelial migration of neutrophils by stimulating a FGFR2/PKA pathway that counteracts selectin- and chemokine-stimulated activation of β2-integrins. These data suggest that FGF23 may be a suitable therapeutic target for inflammation control in patients with CKD.

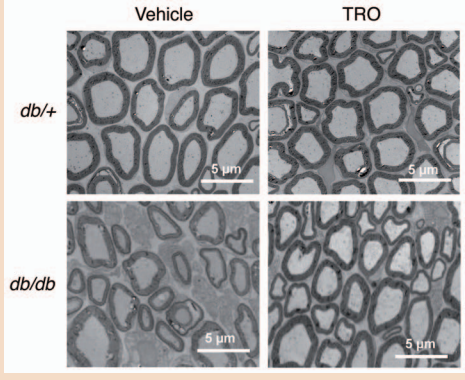
FGF23 signaling impairs neutrophil recruitment and host defense during CKD

Jan Rossaint, Jessica Oehmichen, Hugo Van Aken, Stefan Reuter, Hernann J. Pavenstädt, Melanie Meersch, Mark Unruh, and Alexander Zarbock
http://jci.me/83470

NEUROSCIENCE

Schwann cell mitochondrial calcium leak triggers nerve demyelination

Demyelination is associated with a number of acquired and hereditary peripheral neuropathies, but the molecular mechanisms that trigger demyelination are unknown. In this issue, Sergio Gonzalez and colleagues used fluorescent probes and in vivo multiphoton time-lapse microscopy to document changes in myelinating Schwann cells (SCs) in a murine sciatic nerve crush model. They found that SC demyelination is induced by mitochondrial voltage-dependent anion channel 1–mediated (VDAC1-mediated) calcium release, which activates ERK1/2-, p38-, JNK-, and c-JUN–mediated demyelination pathways. Further, they demonstrated a VDAC1-mediated calcium leak in mitochondria of murine diabetes models, which primes SCs for demyelination, suggesting a mechanism for diabetic peripheral neuropathy. Finally, blocking VDAC1-mediated calcium release prevented demyelination and improved nerve conduction and neuromuscular performance in rodent models of diabetic neuropathy and of Charcot-Marie-Tooth disease (see the accompanying image).



Blocking mitochondrial calcium release in Schwann cells prevents demyelinating neuropathies

Sergio Gonzalez, Jade Berthelot, Jennifer Jiner, Claire Perrin-Tricaud, Ruani Fernando, Roman Chrast, Guy Lenaers, and Nicolas Tricaud
http://jci.me/84505

REVIEWS

Improving vaccine potency with formulation optimization

Modern vaccines must generate a strong, high-quality immune response with minimal toxicity. In order to be effective, vaccine antigens and adjuvants must traffic to the lymph nodes, activate both the innate and adaptive arms of the immune system, and persist for a sufficient amount of time to generate a mature immune response. In this issue, Tyson Moyer, Andrew Zmolek, and Darrell Irvine review recent approaches to tailor and optimize vaccine formulations, which help to control how, when, and where antigens and adjuvants encounter immune cells and tissues. Specifically, they focus on transport of vaccines to lymphoid tissues, delivery of danger signals to immune cells, and the use of materials to regulate the kinetics of subunit vaccine presentation to immune cells.

Beyond antigens and adjuvants: formulating future vaccines
Tyson J. Moyer, Andrew C. Zmolek, and Darrell J. Irvine **http://jci.me/81083**

Mitochondrial dysfunction in lung disease

Mitochondria are essential for energy production via oxidative phosphorylation and also play a key role in nutrient and oxygen sensing as well as cell death and inflammation. Mitochondrial dysfunction is increasingly linked to disease pathogenesis. In this issue, Suzanne Cloonan and Augustine Choi review the role of mitochondrial dysfunction in lung diseases, including chronic obstructive pulmonary disease, pulmonary hypertension, asthma, cystic fibrosis, and lung cancer. At the molecular level, alterations in mitophagy, mitochondrial DNA (mtDNA), second messenger signaling, and the production of mitochondrial damage–associated molecular patterns (mtDAMPs) are features of lung pathogenesis. Such mitochondrial disease signatures are potential targets for diagnosis and therapy for lung diseases.

Mitochondria in lung disease
Suzanne M. Cloonan and Augustine M.K. Choi **http://jci.me/81113**

Going with the flow in vascular health and disease

Mechanical forces play a critical role in the development and function of the cardiovascular system. The blood pumped from the heart exerts pressure, which stretches the walls of blood vessels, and friction force (fluid shear stress), which is parallel to the walls of the blood vessels. The endothelial cells lining the blood vessel walls translate force alterations into biochemical signals that regulate gene expression and cell behavior to mediate normal vascular physiological remodeling; however, these pathways can also contribute to diseases such as atherosclerosis and vascular malformations. Martin Schwartz and colleagues review the basic mechanisms of flow signaling and the alterations in these mechanisms that mediate disease pathogenesis. They propose that atherosclerosis and vascular malformation are essentially diseases in which shear-responsive morphogenetic programs have gone awry, resulting in the generation of abnormal vessels.

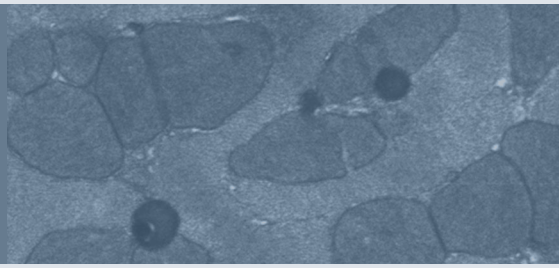
Endothelial fluid shear stress sensing in vascular health and disease
Nicolas Baeyens, Chirosree Bandyopadhyay, Brian G. Coon, Sanguk Yun, and Martin A. Schwartz
http://jci.me/83083

CONVERSATIONS WITH GIANTS IN MEDICINE

Huda Zoghbi

Dr. Huda Zoghbi is a pediatric neurologist, a Howard Hughes Medical Institute investigator; a professor in the departments of Pediatrics, Molecular and Human Genetics, and Neurology and Neuroscience at Baylor College of Medicine; and the founding director of the Jan and Dan Duncan Neurological Research Institute at Texas Children's Hospital. Her work has focused on elucidating the mechanisms underlying Rett syndrome and spinocerebellar ataxia. In an interview with *JCI* Editor-at-Large Ushma Neill, Dr. Zoghbi describes her childhood in Beirut, Lebanon. After her medical studies were interrupted by Lebanon's civil war, Dr. Zoghbi enrolled at Meharry Medical College. She became interested in pediatric neurological disorders during her residency, when she observed many patients with devastating disorders that appeared to have underlying genetic causes. Dr. Zoghbi also describes her discovery of a genetic cause of Rett syndrome, a null mutation in the methyl-CpG binding protein 2 (MeCP2), which researchers are now trying to target therapeutically.
http://jci.me/86445

Journal of Clinical Investigation Consulting Editors



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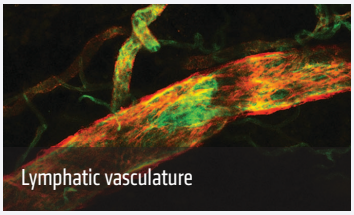


Restoration of lymphatic function rescues obesity in Prox1-haploinsufficient mice

Noelia Escobedo, Steven T. Proulx, Sinem Karaman, Miriam E. Dillard, Nicole Johnson, Michael Detmar, and Guillermo Oliver
http://jci.me/85096

Dynamic dual-isotope molecular imaging elucidates principles for optimizing intrathecal drug delivery

Daniel A. Wolf, Jacob Y. Hesterman, Jenna M. Sullivan, Kelly D. Orcutt, Matthew D. Silva, Merryl Lobo, Tyler Wellman, Jack Hoppin, and Ajay Verma
http://jci.me/85311

Autoimmune response to transthyretin in juvenile idiopathic arthritis

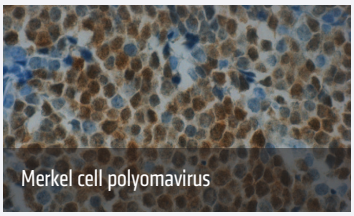
Cristina C. Clement, Halima Moncrieffe, Aditi Lele, Ginger Janow, Aniuska Becerra, Francesco Bauli, Fawzy A. Saad, Giorgio Perino, Cristina Montagna, Neil Cobelli, John Hardin, Lawrence J. Stern, Norman Ilowite, Steven A. Porcelli, and Laura Santambrogio **http://jci.me/85633**

Heme oxygenase-1 regulates mitochondrial quality control in the heart

Travis D. Hull, Ravindra Boddu, Lingling Guo, Cornelia C. Tisher, Amie M. Traylor, Bindiya Patel, Reny Joseph, Sumanth D. Prabhu, Hagir B. Suliman, Claude A. Piantadosi, Anupam Agarwal, and James F. George **http://jci.me/85817**

Glioblastoma-infiltrated innate immune cells resemble M0 macrophage phenotype

Konrad Gabrusiewicz, Benjamin Rodriguez, Jun Wei, Yuuri Hashimoto, Luke M. Healy, Sourindra N. Maiti, Ginu Thomas, Shouhao Zhou, Qianghu Wang, Ahmed Elakkad, Brandon D. Liebelt, Nasser K. Yaghi, Ravesanker Ezhilarasan, Neal Huang, Jeffrey S. Weinberg, Sujit S. Prabhu, Ganesh Rao, Raymond Sawaya, Lauren A. Langford, Janet M. Bruner, Gregory N. Fuller, Amit Bar-Or, Wei Li, Rivka R. Colen, Michael A. Curran, Krishna P. Bhat, Jack P. Antel, Laurence J. Cooper, Erik P. Sulman, and Amy B. Heimberger **http://jci.me/85841**



Survey for human polyomaviruses in cancer

Tuna Toptan, Samuel A. Yousem, Jonhan Ho, Yuki Matsushima, Laura P. Stabile, Maria-Teresa Fernández-Figueras, Rohit Bhargava, Akihide Ryo, Patrick S. Moore, and Yuan Chang
http://jci.me/85562

Mitochondrial protein hyperacetylation in the failing heart

Julie L. Horton, Ola J. Martin, Ling Lai, Nicholas M. Riley, Alicia L. Richards, Rick B. Vega, Teresa C. Leone, David J. Pagliarini, Deborah M. Muoio, Kenneth C. Bedi Jr., Kenneth B. Margulies, Joshua J. Coon, and Daniel P. Kelly **http://jci.me/84897**

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