August 2016
A summary of the most recent articles in The Journal of Clinical Investigation and JCI Insight

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The Harrington Prize for Innovation in Medicine

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THE HARRINGTON PROJECT
FOR DISCOVERY & DEVELOPMENT
Superior function of CAR T cells with checkpoint blockade

Two major approaches to cancer immunotherapy are the use of chimeric antigen receptor (CAR) T cells targeting tumor cell–surface antigens and the administration of antibodies that prevent tumors from dampening antitumor T cell responses; the latter is known as checkpoint blockade. One issue that has limited the utility of CAR T cells for solid tumors is the development of an immunosuppressive tumor microenvironment. In this issue of the JCI, a research team led by Prasad Adusumilli examined two different costimulatory strategies to improve CAR T cell persistence and the role of checkpoint blockade in impairing CAR T cell responses. CAR T cells expressing either the costimulatory signaling domain CD28 or 4-1BB were examined in an orthotopic murine model of pleural mesothelioma. 4-1BB CAR T cells had extended functional cytokine and chemokine secretion; however, both types of CAR T cells eventually became exhausted. The researchers sought to improve the functional persistence of CAR T cells by including checkpoint blockade strategies to inhibit PD-1 signaling. They showed that either adding PD-1–blocking antibodies or using CAR T cells with intrinsic checkpoint blockade mediated by a dominant negative PD-1 receptor improved effector function and overall survival. A Commentary by Xiaopei Huang and Yiping Yang discusses how this study provides a promising approach to targeting solid tumors using combined CAR therapy and checkpoint blockade. The accompanying false-colored electron micrograph shows CAR T cells (blue) attacking and killing cancer cells (magenta).

Human CAR T cells with cell-intrinsic PD-1 checkpoint blockade resist tumor-mediated inhibition

Leonid Cherkassky, Aurore Morello, Jonathan Villena-Vargas, Yang Feng, Dimitar S. Dimitrov, David R. Jones, Michel Sadelain, and Prasad S. Adusumilli  http://jci.me/83092

Related Commentary
Driving an improved CAR for cancer immunotherapy
Xiaopei Huang and Yiping Yang  http://jci.me/88959
c-Abl promotes accumulation of α-synuclein in Parkinsonian model mice

Inherited forms of Parkinson disease (PD) are linked to α-synuclein mutations that produce toxic accumulation of this protein in neurons. Recent reports suggest that inhibiting the nonreceptor tyrosine kinase c-Abl may have neuroprotective effects in PD. In this issue, Saurav Brahmchari and colleagues investigated whether c-Abl regulates α-synuclein accumulation in a mouse model expressing A53T, an α-synuclein mutation associated with familial PD. Overactivation of c-Abl exacerbated α-synuclein accumulation and PD-like symptoms in A53T-expressing mice (see the accompanying image). In contrast, c-Abl deficiency attenuated α-synuclein accumulation and neurodegenerative symptoms. After determining that c-Abl phosphorylates α-synuclein at tyrosine 39 in A53T-expressing mice, an analysis of human postmortem samples confirmed that PD patients exhibit increased phosphotyrosine 39 levels compared with age-matched controls. Together, the results indicate that c-Abl promotes accumulation of α-synuclein in neurons and support the therapeutic potential of c-Abl in PD and related disorders.

Exosome transfer amplifies the immune response to allografts

After transplantation, powerful immune responses that lead to allograft rejection depend on the migration of donor dendritic cells (DCs) to lymphoid tissues, where DCs activate host T cells against the allograft. Quan Liu and coworkers investigated how small populations of donor DCs are able to efficiently generate a host immune response against allografts. In a murine transplantation model, they determined that donor DCs transfer MHC molecules to recipient DCs via exosomes. Recipient DCs that express donor MHC molecules then trigger T cell activation to produce an alloreactive response. Depleting recipient DCs in transplant recipient mice reduced the efficiency of donor MHC molecule presentation to host T cells, delaying acute rejection of allografts. These findings indicate that disrupting the exosome transfer between donor and recipient DCs is a potential strategy for reducing allograft rejection in transplant patients.

Donor dendritic cell-derived exosomes promote allograft-targeting immune response

Quan Liu, Darling M. Rojas-Canales, Sherrie J. Divita, William J. Shufesky, Donna Beer Stolz, Ceza Erdos, Mara L.G. Sullivan, Gregory A. Gibson, Simon C. Watkins, Adriana T. Larregina, and Adrian E. Morelli

http://jci.org/84577
**STEM CELLS**

**Hematopoietic stem cell transplantation prevents degeneration in murine retinitis pigmentosa**

The nervous system cannot replace neurons lost to the degeneration caused by retinitis pigmentosa, but therapeutic advancements to replace lost photoreceptors have the potential to prevent vision impairment and blindness in this disease. Work by Daniela Sanges and colleagues demonstrated that transplantation of hematopoietic stem and progenitor cells (HSPCs) can reprogram retinal Müller glia to differentiate into photoreceptor precursors. Transplantation of HSPCs into degenerative murine retinas induced cell-fusion events that produced Müller-HSPC hybrids. Activation of Wnt signaling drove the hybrids toward a photoreceptor progenitor fate. Moreover, transplantation of Wnt-activated HSPCs in a murine model of retinitis pigmentosa prevented retinal degeneration (see the accompanying image). These results suggest that HSPC transplantation may be a potential strategy for treating retinal degeneration in retinitis pigmentosa.

**Hematology**

**Spinal PKCδ mediates chronic pain in murine sickle cell disease**

Chronic pain is a lifelong symptom of sickle cell disease (SCD), and it is associated with poor patient outcomes. Ying He and colleagues investigated the molecular mechanisms that promote pain in a murine model of SCD. SCD mice exhibited enhanced spontaneous and evoked pain that was linked to increased activation of PKCδ in inhibitory neurons in the spinal cord (see the accompanying image). Silencing PKCδ in these neurons attenuated behavioral indices of pain. Furthermore, a PKCδ-deficient mouse model of SCD developed full SCD phenotypes without exhibiting increased sensitivity to spontaneous or evoked pain. These results indicate that PKCδ may be a pain-promoting mechanism and a promising target for pain therapies in SCD.

**PKCδ-targeted intervention relieves chronic pain in a murine sickle cell disease model**

Ying He, Diana J. Wilkie, Jonathan Nazari, Rui Wang, Robert O. Messing, Joseph DeSimone, Robert E. Molokie, and Zaijie Jim Wang  
http://jci.me/86165

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Netrin-1 fragments promote retinal edema in murine diabetic retinopathy

In diabetic retinopathy (DR), inflammation and disruptions in retinal microvasculature cause swelling in the retina that leads to deterioration of vision. Although current therapies for DR directly target inflammation and pathological vascularization, there is evidence that neuronal guidance molecules may also influence disease development. In a murine model of diabetes, Khalil Miloudi and colleagues determined that fragments of the neuronal guidance molecule netrin-1, but not full-length netrin-1, increased retinal vascular permeability (see the accompanying image). These fragments were formed by matrix metalloproteinase-9 (MMP-9), which is elevated in patients with advanced DR. Inhibition of MMP-9 in a murine model of diabetic retinal edema attenuated retinal vasculature permeability. These findings suggest that preventing the formation of netrin-1 fragments may be an effective strategy for treating DR.

Truncated netrin-1 contributes to pathological vascular permeability in diabetic retinopathy

Khalil Miloudi, François Binet, Ariel Wilson, Agustin Cerani, Malika Oubaha, Catherine Menard, Sullivan Henriques, Gaëlle Mawambo, Agnieszka Dejda, Phuong Trang Nguyen, Flavio A. Rezende, Steve Bourgault, Timothy E. Kennedy, and Przemyslaw Sapieha

http://jci.org/84767

FAMILIAL HYPERCHOLESTEROLEMIA (FH)

Underdiagnosed. Under-treated. Life-threatening

An estimated 1 in 250 Americans (approx. 1.3 million) have FH.³

Lifetime exposure of high LDL-C leads to aggressive atherosclerosis and early heart disease.


www.theFHfoundation.org

The FH Foundation is a patient-centered nonprofit organization dedicated to research, education, and advocacy of Familial Hypercholesterolemia (FH). Our mission is to raise awareness and save lives by increasing the rate of early diagnosis and encouraging proactive treatment. If left untreated, FH leads to aggressive and premature heart disease in women, men and children.
Many risk factors for premature birth share common pathways with cellular senescence. Mice with a uterine-specific deletion of p53 (p53<sup>−/−</sup> mice) experience early senescence of the uterine decidua that triggers premature parturition. Previous work has shown that mTORC1 inhibition can reduce incidence of premature parturition in p53<sup>−/−</sup> mice, but the mechanisms linking mTORC1 signaling and parturition timing are unclear. In this issue, Wenbo Deng and colleagues observed that treating pregnant p53<sup>−/−</sup> mice with the antidiabetic drug metformin or the antioxidant resveratrol attenuated decidual senescence and premature parturition (see the accompanying image). These effects were associated with activation of AMPK and inhibition of mTORC1 signaling. Mechanistically, they found that p53 and sestrins integrate AMPK and mTORC1 signaling to coordinate parturition timing. The findings indicate that targeting the sestrin/AMPK/mTORC1 pathway is a potential therapeutic strategy for improving decidual health and reducing incidence of premature birth.

p53 coordinates decidual sestrin 2/AMPK/mTORC1 signaling to govern parturition timing
Wenbo Deng, Jeeyon Cha, Jia Yuan, Hirofumi Haraguchi, Amanda Bartos, Emma Leishman, Benoit Viollet, Heather B. Bradshaw, Yasushi Hirota, and Sudharsu K. Dey  http://jci.me/87715

AMPK and mTORC1 coordinate to determine parturition timing

Statin treatment may improve pregnancy outcomes in refractory antiphospholipid syndrome

Pregnant women who suffer from antiphospholipid syndrome (APS) are at risk of developing severe complications, such as preeclampsia and intrauterine growth restriction (IUGR) that lead to premature birth. Low-dose aspirin plus low-molecular-weight heparin (LDA+LMWH) is a conventional treatment for APS in pregnant women, but fails to prevent preeclampsia and IUGR in many patients. Eleftheria Lefkou and colleagues observed that treating pregnant p53<sup>−/−</sup> mice with the antidiabetic drug pravastatin improves pregnancy outcomes in obstetric antiphospholipid syndrome refractory to antithrombotic therapy
Eleftheria Lefkou, Apostolos Mamopoulos, Themistoklis Dagklis, Christos Vasnakis, David Roussos, and Guillemirina Girardi  http://jci.me/86957

p21 downregulates IFN-β to modulate macrophage reprogramming

In sepsis, systemic bacterial infection can overstimulate the immune system, leading to an immunosuppressive state that is linked to an increased risk of secondary infections and death. This response is mediated in part by compensatory reprogramming of proinflammatory M1 macrophages to an antiinflammatory M2 macrophage-like phenotype. A study by Gorjana Rackov and colleagues determined that the shift in M1-to-M2 homeostasis depends on p21 expression. In murine M1 macrophages, p21 downregulated IFN-β to induce a hyporesponsive state that was independent of its cell cycle–inhibiting effect. This finding was corroborated in monocytes from sepsis patients, which displayed lower IFN-β levels and elevated p21 expression compared with monocytes from healthy patients. The study indicates that p21 contributes to a deleterious immunosuppressive response to sepsis by regulating the balance between proinflammatory and antiinflammatory macrophage function.

p21 mediates macrophage reprogramming through regulation of p50-p50 NF-κB and IFN-β

p21 downregulates IFN-β to modulate macrophage reprogramming

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p21 mediates macrophage reprogramming through regulation of p50-p50 NF-κB and IFN-β

Pravastatin improves pregnancy outcomes in obstetric antiphospholipid syndrome refractory to antithrombotic therapy
Eleftheria Lefkou, Apostolos Mamopoulos, Themistoklis Dagklis, Christos Vasnakis, David Roussos, and Guillemirina Girardi  http://jci.me/86957

Related Commentary
Pravastatin to prevent obstetrical complications in women with antiphospholipid syndrome
Maged M. Costantine  http://jci.me/89137
Transcription factor RelA regulates oncogene-induced senescence in murine pancreatic tumors

Few effective therapeutic agents exist to treat pancreatic ductal adenocarcinoma (PDAC), and the disease is associated with a dismal prognosis. Although recent drug discovery approaches have focused on targeting the IκB kinase/NF-κB (IKK/NF-κB) pathway in cancer therapies, the NF-κB subunit RelA has not received much attention. Marina Lesina and colleagues determined that RelA is a tumor barrier that opposes IKK complex function in pancreatic carcinogenesis. In a murine model of pancreatic cancer, loss of RelA accelerated tumor proliferation (see the accompanying image). The researchers then identified RelA as a central regulator of oncogene-induced senescence through CXCR2/CXCL1 signaling pathways. Further, the findings describe a dual stage-specific function of RelA in PDAC. In the accompanying Commentary, Murray Korc discusses the implications of these findings for the clinical application of cancer therapies that target NF-κB and CXCR2.

RelA regulates CXCL1/CXCR2-dependent oncogene-induced senescence in murine Kras-driven pancreatic carcinogenesis

Related Commentary
RelA: a tale of a stitch in time
Murray Korc http://jci.me/89156

Common BRCA1 founder mutation mediates treatment resistance in breast cancer

Germline mutations in BRCA1 are one of the most common genetic factors that predispose women to breast and ovarian cancers. Although tumors that harbor mutant BRCA1 alleles initially respond well to PARP inhibitors and platinum-based chemotherapies, the tumors eventually become resistant to these treatments. This month, two studies in the JCI investigate the underlying mechanisms of treatment resistance in a common BRCA1 founder mutation, the BRCA1185delAG allele. Rinske Drost and colleagues discovered that a murine variant of the BRCA1 185delAG allele expressed a BRCA1 protein that lacked a RING domain. Loss of the RING domain predicted poor treatment responses in both murine and human tumors. A study by Yifan Wang and colleagues examined treatment resistance in BRCA1185delAG-expressing breast cancer cells and determined that a hypomorphic, RING-deficient BRCA1 protein was responsible for loss of sensitivity to DNA-damaging therapies. In the accompanying Commentary, Simon Powell discusses the implications of these findings for existing and potential breast and ovarian cancer therapies.

Related Research
BRCA1185delAG tumors may acquire therapy resistance through expression of RING-less BRCA1

RING domain–deficient BRCA1 promotes PARP inhibitor and platinum resistance

Related Commentary
BRCA1 loses the ring but lords over resistance
Simon N. Powell http://jci.me/89209
The role of genomic dark matter in cancer

Within the last decade, non-protein-coding transcription, which represents 60%–70% of the human genome, has gone from being regarded as transcriptional noise to a potential source of critical genomic regulators. Long noncoding RNAs (lncRNAs) are transcribed in a manner similar to that of protein-coding genes, and recent unbiased genome-wide searches have identified thousands of lncRNAs. In this Review, Joseph Evans, Felix Feng, and Arul Chinnaiyan detail the emergence of lncRNAs as critical regulators of oncogenic signaling pathways. RNA sequencing of patient tumor samples identified nearly 8,000 cancer-specific lncRNAs. Individual lncRNAs have now been shown to play a role in the p53 pathway, hypoxia responses, the epithelial-to-mesenchymal transition, telomere maintenance, and hormone receptor signaling. Furthermore, lncRNAs are being developed as diagnostic and prognostic biomarkers, and the US Food and Drug Administration recently approved a urine test for prostate cancer–specific lncRNAs (see the accompanying image).

The bright side of dark matter: lncRNAs in cancer
Joseph R. Evans, Felix Y. Feng, and Arul M. Chinnaiyan  http://jci.me/84421

Modeling long noncoding RNA function in vivo

Nearly three-quarters of the mammalian genome is transcribed into RNA, but only a fraction of these transcripts encode proteins. Long noncoding RNAs (lncRNAs), which are longer than 200 nucleotides, are known to markedly impact the expression of protein-coding genes and are required for processes such as X chromosome inactivation. The number of lncRNAs has grown rapidly; however, our understanding of their underlying molecular mechanisms and their functions in vivo remain limited due to a dearth of animal models in which lncRNA expression or function has been manipulated. In this issue, Michael Feyder and Loyal Goff review the use of animal models to profile lncRNA expression, evaluate different strategies to manipulate lncRNA expression or function (see the accompanying image), and discuss the phenotypes that have been attributed to lncRNAs thus far.

Investigating long noncoding RNAs using animal models
Michael Feyder and Loyal A. Goff  http://jci.me/84422

CONVERSATIONS WITH GIANTS IN MEDICINE

Laurie Glimcher

Laurie Glimcher is a world-class immunologist who discovered the transcription factors that direct immune cell activation. She has also made important advancements in clinical practice and research initiatives as the dean of Weill Cornell Medical School. In January 2017, she will become the president and CEO of the Dana-Farber Cancer Institute. Dr. Glimcher talks about her path to becoming a physician-scientist in an interview with Editor-at-Large Ushma Neill. She discusses her early training and research at Harvard Medical School and the NIH and describes her serendipitous discovery of the anabolic pathway for Schnurri-3, an essential regulator of bone formation that is being investigated as an important therapeutic target for osteoporosis.  http://jci.me/88964
Detection of pancreatic ductal adenocarcinoma-associated repeat RNAs in patient sera

Pancreatic ductal adenocarcinoma (Pdac) is a leading cause of cancer death. Most patients are diagnosed with advanced disease, and there is a critical need for biomarkers that can detect the disease at earlier stages. Takahiro Kishikawa and colleagues developed a convenient method to quantify aberrantly expressed satellite repeat RNAs in patient sera, as human satellite II RNA is specifically expressed at high levels in human Pdacs compared with normal tissues. Using tandem repeat amplification with nuclease protection–digital droplet PCR (TRAP-ddPCR), Kishikawa and colleagues analyzed sera from Pdac patients and controls. Measurement of HSATII RNA allowed for discrimination between Pdac patients and controls with nonneoplastic conditions, such as autoimmune pancreatitis, as well as patients with intraductal papillary mucinous neoplasms, a precancerous lesion. These studies indicate that this method could potentially be used to screen for early-stage Pdac.

Quantitation of circulating satellite RNAs in pancreatic cancer patients
Takahiro Kishikawa, Motoyuki Otsuka, Takeshi Yoshikawa, Motoko Ohno, Keisuke Yamamoto, Natsuyo Yamamoto, Ai Katani, and Kazuhiko Koike
http://jci.me/86646

Immune checkpoint blockade and radiotherapy: a one-two punch for lung cancer

Radiotherapy (RT) is a common nonsurgical treatment for patients with non–small-cell lung carcinoma (NSCLC) that induces tumor cell death and frequently results in regression; however, many patients later suffer from relapse or metastasis. Because RT promotes an inflammatory environment that can trigger antitumor immune responses, therapies that augment immune responses could potentially increase RT efficacy. Using a genetically engineered mouse model of Kras-driven NSCLC, Grit Herter-Sprie, Shohei Koyama, and colleagues demonstrate that the addition of antibodies targeting the immune checkpoint programmed cell death 1 (PD1) markedly enhanced RT antitumor effects (see the accompanying image). Notably, anti-PD1 therapy was not efficacious in either tumors previously treated with RT or tumors lacking the tumor suppressor STK11. These studies indicate that this therapeutic combination may be efficacious in NSCLC patients.

Synergy of radiotherapy and PD-1 blockade in Kras-mutant lung cancer
http://jci.me/87415
Inhibition of glutathione-S-transferase \( \pi \) attenuates lung fibrosis in mice

Idiopathic pulmonary fibrosis (IPF) is characterized by apoptosis of airway epithelial cells, leading to the release of factors that cause fibrotic remodeling of the airways and diminished lung function. Apoptosis is partially dependent on cellular redox status, and decreases in the antioxidant and free radical scavenger glutathione (GSH) have been reported in IPF patients, leading David McMillan and colleagues to explore the role of the cysteine-targeted posttranslational modification protein S-glutathionylation (PSSG) in IPF. McMillan and colleagues demonstrate that genetic or pharmacologic inhibition of glutathione-S-transferase \( \pi \) (GSTP) attenuates bleomycin- or TGF-\( \beta \)-induced pulmonary fibrosis (see the accompanying image), caspase activation, and PSSG. These data indicate that GSTP is a mediator of fibrosis and may be a suitable therapeutic target in IPF.

Attenuation of lung fibrosis in mice with a clinically relevant inhibitor of glutathione-S-transferase \( \pi \)


http://jci.me/85717

Repurposing tromethamine to treat cystic fibrosis airway disease

The airway surface liquid (ASL) helps protect the lungs against pathogens, and the appropriate ASL volume, pH, and ionic composition are required for optimal airway defense. Cystic fibrosis (CF) is caused by expression of a dysfunctional CF transmembrane conductance regulator (CFTR), which acidifies the ASL and renders people with CF more susceptible to lung infections. Joseph Zabner and colleagues examined the effect of tromethamine, a drug that is currently approved to treat metabolic acidosis, on ASL pH and bacterial killing activity. They demonstrated that inhalation of aerosolized tromethamine raised ASL pH in both pigs and people with CF. Importantly, tromethamine enhanced bacterial killing in the airways of pigs with CF and in sputum samples from people with CF. These studies indicate that tromethamine may have therapeutic benefits in CF airway disease.

Repurposing tromethamine as inhaled therapy to treat CF airway disease

Mahmoud H. Abou Alaiwa, Janice L. Launspach, Kelsey A. Sheets, Jade A. Rivera, Nicholas D. Gansemer, Peter J. Toft, Peter S. Thorne, Michael J. Welsh, David A. Stultz, and Joseph Zabner  

http://jci.me/87535

Enzyme replacement therapy for children with hypophosphatasia

Hypophosphatasia (HPP) is an inborn error of metabolism caused by loss-of-function mutations in the gene that encodes the tissue-nonspecific isoenzyme of alkaline phosphatase (TNSALP). Deficiency of TNSALP in children can result in rickets: skeletal pain, deformity, and fractures; muscle weakness; and premature loss of deciduous teeth. Michael Whyte and colleagues conducted a clinical trial in 12 pediatric HPP patients, ages 6–12, to evaluate the safety and efficacy of asfotase alfa, a recombinant, bone-targeted, human TNSALP administered by s.c. injection. During 5 years of treatment with asfotase alfa, patients exhibited marked skeletal improvements compared with HPP historical controls — as well as improvements in growth, strength, agility, motor function, and quality of life — eventually resembling healthy age- and sex-matched peers. Although patients developed antibodies to asfotase alfa, they did not show treatment resistance, and there were no serious adverse events. The US FDA designated asfotase alfa a breakthrough therapy for HPP in October 2015.

Asfotase alfa therapy for children with hypophosphatasia


http://jci.me/85971
AIDS/HIV
Stem-loop binding protein is a multifaceted cellular regulator of HIV-1 replication
Ming Li, Lynne D. Tucker, John M. Asara, Collins K. Cheruvuiot, Huafei Lu, Zhijin J. Wu, Michael C. Newstein, Mark S. Dooner, Jennifer Friedman, Michelle A. Lally, and Bharat Ramratnam
http://jci.me/82360

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Truncated netrin-1 contributes to pathological vascular permeability in diabetic retinopathy
Khalil Miloudi, François Binet, Ariel Wilson, Agustin Cerani, Malika Dubaha, Catherine Menard, Sullivan Henriques, Gaelle Mawambo, Agnieszka Dejda, Phuong Trang Nguyen, Flavio A. Rezende, Steve Bourgault, Timothy E. Kennedy, and Przemyslaw Sapieha
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Induced superficial chondrocyte death reduces catabolic cartilage damage in murine posttraumatic osteoarthritis
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http://jci.me/83676

CARDIOLOGY
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http://jci.me/85350

Developmental SHP2 dysfunction underlies cardiac hypertrophy in Noonan syndrome with multiple lentigines
http://jci.me/80396

GENETICS
Destabilized SMCS/6 complex leads to chromosome breakage syndrome with severe lung disease
http://jci.me/82890

Natural allelic variation of the IL-21 receptor modulates ischemic stroke infarct volume
Han Kyu Lee, Sehoon Keum, Huaxin Sheng, David S. Warner, Donald C. Lo, and Douglas A. Marchuk
http://jci.me/84491

EPHB4 kinase–inactivating mutations cause autosomal dominant lymphatic-related hydrops fetalis
http://jci.me/85794

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PKCδ-targeted intervention relieves chronic pain in a murine sickle cell disease model
Ying He, Diana J. Wilkie, Jonathan Nazari, Rui Wang, Robert D. Messing, Joseph DeSimone, Robert E. Molokie, and Zaijie Jim Wang
http://jci.me/86165

IMMUNOLOGY
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http://jci.me/83404

METABOLISM
IRF3 promotes adipose inflammation and insulin resistance and represses browning
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http://jci.me/86080

Apoc-III inhibits clearance of triglyceride-rich lipoproteins through LDL family receptors
http://jci.me/86610

MICROBIOLOGY
Pneumococcal meningitis is promoted by single cocci expressing pilus adhesin RrgA
Federico Lovino, Dina L. Hammarlóf, Genevieve Garriss, Sarah Brovall, Priyanka Nannapaneni, and Birgitta Henriques-Normark
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Tandem CAR T cells targeting HER2 and IL13Rα2 mitigate tumor antigen escape

E2f8 mediates tumor suppression in postnatal liver development

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The nonsense-mediated RNA decay pathway is disrupted in inflammatory myofibroblastic tumors

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Donor dendritic cell–derived exosomes promote allograft-targeting immune response ▶ p. 2

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TBX4 regulates myofibroblast accumulation and lung fibrosis

myofibroblast accumulation and lung fibrosis

pancreatic carcinogenesis

RNF120 promotes tumourigenic PanIN-type 4 and 6, leading to ductal adenocarcinoma

myofibroblast accumulation and lung fibrosis

pancreatic carcinogenesis

myofibroblast accumulation and lung fibrosis
ISL1 cardiovascular progenitor cells for cardiac repair after myocardial infarction
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Dual epithelial and immune cell function of Dvl1 regulates gut microbiota composition and intestinal homeostasis

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Deep sequencing reveals microRNAs predictive of antiangiogenic drug response
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Perinatal tolerance to proinsulin is sufficient to prevent autoimmune diabetes

The MEK inhibitor trametinib separates murine graft-versus-host disease from graft-versus-tumor effects
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Prohibitin/annexin 2 interaction regulates fatty acid transport in adipose tissue
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Recognition of influenza H3N2 variant virus by human neutralizing antibodies

An extra copy of p53 suppresses development of spontaneous Kras-driven but not radiation-induced cancer
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Mutant p53 regulates ovarian cancer transformed phenotypes through autocrine matrix deposition

Profiling cancer testis antigens in non–small-cell lung cancer

Transplantation of human skin microbiota in models of atopic dermatitis
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