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

ALSO IN THIS ISSUE:
Epigenetic regulation of erythropoietin 7
A humanized Morris water maze 9
Review Series: HIV edited by Robert F. Siliciano 10
Introducing JCI Insight 13

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Metabolic reprogramming in the metastatic niche p. 6
The JCI welcomes submissions in the following categories:

Research:
Substantial new mechanistic insights into biology and disease.

Sample article: Hepatic stellate cells contribute to progenitor cells and liver regeneration
Claus Kordes, Iris Sawitza, Silke Götze, Diran Herebian, and Dieter Häussinger
Published November 2014  http://jci.me/74119
Times cited: 21

Clinical medicine:
Research that reports early-stage, effective new therapies that impact disease outcomes in patients.

Sample article: Umbilical cord blood expansion with nicotinamide provides long-term multilineage engraftment
Published June 2014  http://jci.me/74556
Times cited: 23

Brief report:
Discrete, highly significant findings in a short format.

Sample article: Early microbial translocation blockade reduces SIV-mediated inflammation and viral replication
Jan Kristoff, George Haret-Richter, Dongzhu Ma, Ruy M. Ribeiro, Culling Xu, Elaine Cornell, Jennifer L. Stock, Tianyu He, Adam D. Mobley, Samantha Ross, Anita Trichel, Cara Wilson, Russell Tracy, Alan Landay, Cristian Apetrei, and Ivona Pandrea
Published May 2014  http://jci.me/75090
Times cited: 18

More information: http://jci.me/aqcqs or editors@the-jci.org

Citation information is from Web of Science and Scopus as of December 2015.
We are delighted to publish the first set of articles in JCI Insight, the newest peer-reviewed publication of the American Society for Clinical Investigation (ASCI). In creating this journal, we sought to provide an expanded forum for a wide range of preclinical, translational, and clinical research that uncovers new insights into the basis of disease and therapeutic approaches. In selecting articles for JCI Insight, we place a strong emphasis on rigorous experimental methods and data reporting, which are truly the hallmark of publications in the JCI family.

In January 2016, JCI Insight opened to new submissions. Manuscripts that meet our editorial bar for quality and interest to our readership are sent for external peer review by our professional editors. We are indebted to our esteemed board of consulting editors, who have agreed to provide advice on manuscripts in their area of expertise. We have also implemented a transfer process for manuscripts previously considered at the JCI that we believe are better suited for JCI Insight. For manuscripts that have been previously reviewed at the JCI, the submission and reviewer comments are transferred to JCI Insight, allowing our editors to come to a rapid decision based on the original evaluation.

In the first batch of articles, we are extremely proud to publish an outstanding collection of preclinical and clinical research from around the globe (see page 13 for a listing of the articles). We are pleased to provide this new venue for the publication of well-executed human and preclinical model-based research, and we encourage you to consider JCI Insight for your work within this scope.

For more information about submitting manuscripts to JCI Insight, please visit our website: www.insight.jci.org.

Sarah Jackson
Executive Editor

The Journal of Clinical Investigation and JCI Insight

To read Dr. Jackson’s complete editorial, see http://jci.me/86444.
Research articles in the current issue of the JCI

Bone biology

**Osteoblast-derived VEGF regulates osteoblast differentiation and bone formation during bone repair**

Kai Hu and Bjorn R. Olsen  
[http://jci.me/82585](http://jci.me/82585)

Endocrinology

**CYP24 inhibition as a therapeutic target in FGF23-mediated renal phosphate wasting disorders**

Xiuying Bai, Dengshun Miao, Sophia Xiao, Dinghong Qiu, René St-Arnaud, Martin Petkovich, Ajay Gupta, David Goltzman, and Andrew C. Karaplis  
[http://jci.me/81928](http://jci.me/81928)

With related Commentary by Valentin David and Myles Wolf  
More, p. 8

Gastroenterology

**Toll-like receptor 4–mediated lymphocyte influx induces neonatal necrotizing enterocolitis**

Charlotte E. Egan, Chhinder P. Sodhi, Misty Good, Joyce Lin, Hongpeng Jia, Yukihiro Yamaguchi, Peng Lu, Congrong Ma, Maria F. Branca, Samantha Weyandt, William B. Fulton, Diego F. Niño, Thomas Prindle Jr., John A. Ozolek, and David J. Hackam  
[http://jci.me/83356](http://jci.me/83356)

**Rho-A prenylation and signaling link epithelial homeostasis to intestinal inflammation**

Rocío López-Posadas, Christoph Becker, Claudia Günther, Stefan Tenzer, Kerstin Amann, Ulrike Billmeier, Raja Atreya, Gionata Fiorino, Stefania Vetrano, Silvio Danese, Arif B. Ekici, Stefan Wirtz, Veronika Thonn, Alastair J.M. Watson, Cord Brakebusch, Martin Bergö, Markus F. Neurath, and Imke Atreya  
[http://jci.me/80997](http://jci.me/80997)

Genetics

**Molecular etiology of arthrogryposis in multiple families of mostly Turkish origin**

[http://jci.me/84457](http://jci.me/84457)
Hematology

A chimeric platelet-targeted urokinase prodrug selectively blocks new thrombus formation
http://jci.me/81470

Immunology

Transcription factor ICBP90 regulates the MIF promoter and immune susceptibility locus
Jie Yao, Lin Leng, Maor Sauler, Weiling Fu, Junsong Zheng, Yi Zhang, Xin Du, Xiaqing Yu, Patty Lee, and Richard Bucala
http://jci.me/81937

Broadly neutralizing anti-influenza antibodies require Fc receptor engagement for in vivo protection
David J. DiLillo, Peter Palese, Patrick C. Wilson, and Jeffrey V. Ravetch
http://jci.me/84428

Muscle biology

The AMPK-related kinase SNARK regulates muscle mass and myocyte survival
Sarah J. Lessard, Donato A. Rivas, Kawai So, Ho-Jin Koh, André Lima Queiroz, Michael F. Hirshman, Roger A. Fielding, and Laurie J. Goodyear
http://jci.me/79197

Nephrology

DNA methyltransferase inhibition restores erythropoietin production in fibrotic murine kidneys
Yu-Ting Chang, Ching-Chin Yang, Szu-Yu Pan, Yu-Hsiang Chou, Fan-Chi Chang, Chun-Fu Lai, Ming-Hsuan Tsai, Huan-Lun Hsu, Ching-Hung Lin, Wen-Chih Chiang, Ming-Shiou Wu, Tzong-Shinn Chu, Yung-Ming Chen, and Shuei-Liong Lin
http://jci.me/82819

Neuroscience

Cross-species translation of the Morris maze for Alzheimer’s disease
Katherine L. Possin, Pascal E. Sanchez, Cliff Anderson-Bergman, Roland Fernandez, Geoffrey A. Kerchner, Erica T. Johnson, Allyson Davis, Iris Lo, Nicholas T. Bott, Thomas Kiely, Michelle C. Fenesey, Bruce L. Miller, Joel H. Kramer, and Steven Finkbeiner
http://jci.me/78464

With related Commentary by Kerin K. Higa, Jared W. Young, and Mark A. Geyer
http://jci.me/81950

CXCL13 drives spinal astrocyte activation and neuropathic pain via CXCR5
Bao-Chun Jiang, De-Li Cao, Xin Zhang, Zhi-Jun Zhang, Li-Na He, Chun-Hua Li, Wen-Wen Zhang, Xiao-Bo Wu, Temugin Berta, Ru-Rong Ji, and Yong-Jing Gao
http://jci.me/81950
Research articles in the current issue of the JCI

Neuroscience

Activating transcription factor 6 derepression mediates neuroprotection in Huntington disease
José R. Naranjo, Hongyu Zhang, Diego Villar, Paz González, Xose M. Dopazo, Javier Morón-Oset, Elena Higueras, Juan C. Oliveros, María D. Arrabal, Angela Prieto, Pilar Cercós, Teresa González, Alicia De la Cruz, Juan Casado-Vela, Alberto Rábano, Carmen Valenzuela, Marta Gutierrez-Rodríguez, Jia-Yi Li, and Britt Mellström
http://jci.me/82670

Prostaglandin-dependent modulation of dopaminergic neurotransmission elicits inflammation-induced aversion in mice
Michael Fritz, Anna M. Klawonn, Anna Nilsson, Anand Kumar Singh, Joanna Zajdel, Daniel Björk Wilhelms, Michael Lazarus, Andreas Löfberg, Maarit Jaarola, Unn Ørtegren Kugelberg, Timothy R. Billiar, David J. Hackam, Chhinder P. Sodhi, Matthew D. Breyer, Johan Jakobsson, Markus Schwaninger, Günther Schütz, Jan Rodríguez Parkitna, Clifford B. Saper, Anders Blomqvist, and David Engblom
http://jci.me/83844

Oncology

Histone demethylase JMJD2A drives prostate tumorigenesis through transcription factor ETV1
Tae-Dong Kim, Fang Jin, Sook Shin, Sangphil Oh, Stan A. Lightfoot, Joseph P. Grande, Aaron J. Johnson, Jan M. van Deursen, Jonathan D. Wren, and Ralf Janknecht
http://jci.me/78132

Nuclear pore protein NUP88 activates anaphase-promoting complex to promote aneuploidy
Ryan M. Naylor, Karthik B. Jeganathan, Xiuqi Cao, and Jan M. van Deursen
http://jci.me/82277

Tetraspanin CD37 protects against the development of B cell lymphoma
Charlotte M. de Winde, Sharon Veenbergen, Ken H. Young, Zijun Y. Xu-Monette, Xiaoxiao Wang, Yi Xia, Kausar J. Jabbar, Michiel van den Brand, Alie van der Schaaf, Suraya Elfrink, Inge S. van Houdt, Marion J. Gijbels, Fons A.J. van de Loo, Miranda B. Bennink, Konnie M. Hebeda, Patricia J.T.A. Groenen, J. Han van Krieken, Carl G. Fiegdo, and Annemieke B. van Spriel
http://jci.me/81041

The transcription factor BACH2 promotes tumor immunosuppression
Rahul Roychoudhuri, Robert L. Eil, David Clever, Christopher A. Klebanoff, Madhusudhanan Sukumar, Francis M. Grant, Zhiya Yu, Gautam Mehta, Hui Liu, Ping Jin, Yun Ji, Douglas C. Palmer, Jenny H. Pan, Anna Chichura, Joseph G. Crompton, Shashank J. Patel, David Strongek, Ena Wang, Francesco M. Marincola, Klaus Okkenhaug, Luca Gattinoni, and Nicholas P. Restifo
http://jci.me/82884

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CCAT1 is an enhancer-templated RNA that predicts BET sensitivity in colorectal cancer
Mark L. McLeodland, Kathryn Mesh, Edward Lorenzana, Vivek S. Chopra, Ehud Segal, Colin Watanabe, Benjamin Haley, Oleg Mayba, Murat Yaylaoglu, Florian Gnad, and Ron Firestein
http://jci.me/83265

Wnt5a induces ROR1/ROR2 heterooligomerization to enhance leukemia chemotaxis and proliferation
Jian Yu, Liguang Chen, Bing Cui, George F. Widhopf II, Zhouxin Shen, Rongrong Wu, Ling Zhang, Suping Zhang, Steven P. Briggs, and Thomas J. Kipps
http://jci.me/83535

PKLR promotes colorectal cancer liver colonization through induction of glutathione synthesis
Alexander Nguyen, Jia Min Loo, Rohit Mital, Ethan M. Weinberg, Fung Ying Man, Zhaoshi Zeng, Philip B. Paty, Leonard Saltz, Yelena Y. Janjiejan, Elisa de Stanchina, and Sohail F. Tavazoie
http://jci.me/83587

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**TAP-independent self-peptides enhance T cell recognition of immune-escaped tumors**
Elien M. Doorduijn, Marjolein Sluijter, Bianca J. Querido, Cláudia C. Oliveira, Adnane Achour, Ferry Ossendorp, Sjoerd H. van der Burg, and Thorbald van Hall

http://jci.me/83671

With related Commentary by Rolf Kiessling

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**Pulmonology**

**Placenta growth factor augments airway hyperresponsiveness via leukotrienes and IL-13**
Marthe-Sandrine Eiymo Mwa Mpollo, Eric B. Brandt, Shiva Kumar Shanmukhappa, Paritha I. Arumugam, Swati Tiwari, Anastacia Loberg, Devin Pillis, Tilat Rizvi, Mark Lindsey, Bart Jonck, Peter Carmeliet, Vijay K. Kaira, Timothy D. Le Cras, Nancy Ratner, Marsha Wills-Karp, Gurjit K. Khurana Hershey, and Punam Malik

http://jci.me/77250

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**Stem cells**

**TGF-β/β2-spectrin/CTCF-regulated tumor suppression in human stem cell disorder Beckwith-Wiedemann syndrome**

http://jci.me/80937
The liver is a frequent site of metastasis of colorectal cancers. Approximately 60 percent of patients with colorectal cancer will develop a liver metastasis, which is associated with poor prognosis, prompting Sohail Tavazoie and colleagues to investigate the mechanisms responsible for driving secondary liver tumors. Using a large-scale shRNA drop-out screen in three different colon cancer cell lines, they identified a requirement for liver and red blood cell pyruvate kinase (PKLR) for liver colonization after direct injection of cells into the liver. The researchers subsequently showed higher PKLR expression in patient metastases compared with that in primary colorectal tumors. Mass spectrometric identification of PKLR-binding partners revealed an association with the PKM2 isoform of pyruvate kinase, which has dual roles in cancer, both driving aerobic glycolysis and also limiting the reducing potential of cells to withstand ROS damage. Biochemically, PKLR was found to repress PKM2, and loss of PKLR led to decreased levels of the antioxidant glutathione. Further, small-molecule inhibition of glutathione synthesis also decreased the ability of colon cancer cells to colonize the liver in mice. Taken together, these findings indicate that PKLR promotes metastatic progression by inhibiting PKM2 enzymatic activity and suggest a common pathway that can be therapeutically targeted across a broad spectrum of colorectal cancers.

The accompanying image shows a tumor nodule from PKLR-depleted tumor cells (luciferase, green), with few cells in the nodule core and increased numbers of apoptotic cells (cleaved caspase-3, red). Nuclei are stained with DAPI.

**PKLR promotes colorectal cancer liver colonization through induction of glutathione synthesis**

Alexander Nguyen, Jia Min Loo, Rohit Mital, Ethan M. Weinberg, Fung Ying Man, Zhaoshi Zeng, Philip B. Poty, Leonard Saltz, Yelena Y. Janjigian, Elisa de Stanchina, and Sohail F. Tavazoie

[http://jci.me/83587](http://jci.me/83587)
Transcription factor BACH2 suppresses antitumor immunity

Progression of cancer in immunocompetent individuals requires that antitumor immune responses are suppressed. Multiple immune cell lineages contribute to immunosuppression in cancer, but the molecular mechanisms underlying development of these lineages are unclear. In this issue, Rahul Roychoudhuri and colleagues demonstrate that the transcription factor BACH2, which regulates the differentiation of multiple cellular lineages of the innate and adaptive immune systems, is required to establish immunosuppression within tumors. Loss of Bach2 in mice activated innate and adaptive immunity within tumors, resulting in impaired tumor growth. Mechanistically, BACH2 promoted tumor immunosuppression through CD4+ Treg-mediated inhibition of intratumoral CD8+ T cells and the inflammatory cytokine IFN-γ. These results indicate that BACH2 is a potential therapeutic target to disrupt immunosuppression in cancer.

The transcription factor BACH2 promotes tumor immunosuppression
Rahul Roychoudhuri, Robert L. Eil, David Clever, Christopher A. Klebanoff, Madhusudhanan Sukumar, Francis M. Grant, Zhiya Yu, Gautam Mehta, Hui Liu, Ping Jin, Yun Ji, Douglas C. Palmer, Jenny H. Pan, Anna Chichura, Joseph G. Crompton, Shashank J. Patel, David Stroncek, Ena Wang, Francesco M. Marincola, Klaus Okkenhaug, Luca Gattinoni, and Nicholas P. Restifo http://jci.me/82884

Patients with chronic kidney disease (CKD) frequently develop anemia due to poor production of erythropoietin (EPO). Renal EPO-producing cells are present in CKD kidneys, but, while these cells can make EPO, they do not respond appropriately to hypoxic stimuli. In this issue, Yu-Ting Chang and colleagues show that fibroblast-like kidney pericytes produce EPO through a HIF2α-mediated mechanism but EPO production is repressed when these cells differentiate into myofibroblasts, as occurs in CKD. Myofibroblasts upregulate DNA methytransferases (see the accompanying image), which hypermethylate DNA to suppress gene expression. Chang and colleagues found that the Epo promoter was hypermethylated in kidney myofibroblasts. Importantly, treatment with the DNA methyltransferase inhibitor 5-azacytidine restored EPO expression and ameliorated anemia in a murine CKD model.

DNA methyltransferase inhibition restores erythropoietin production in fibrotic murine kidneys
Yu-Ting Chang, Ching-Chin Yang, Szu-Yu Pan, Yu-Hsiang Chou, Fan-Chi Chang, Chun-Fu Lai, Ming-Hsuan Tsai, Huan-Lun Hsu, Ching-Hung Lin, Wen-Chih Chiang, Ming-Shiou Wu, Tzong-Shinn Chu, Yung-Ming Chen, and Shuei-Liong Lin http://jci.me/82819
CYP24A1 inhibition ameliorates skeletal abnormalities associated with FGF23-mediated renal phosphate wasting

The mitochondrial enzyme CYP24A1 initiates the degradation of the physiologically active form of vitamin D₃. Long-lasting and/or elevated expression of CYP24A1 is hypothesized to contribute to the pathology of diseases that could potentially be ameliorated by vitamin D administration. Xiuying Bai and colleagues demonstrate that FGF23-mediated renal phosphate wasting and hypophosphatemic osteomalacia are associated with increased CYP24 expression. Deletion of Cyp24 in two mouse strains with high circulating levels of FGF23 resulted in a near-complete reversal of rachitic/osteomalacic bone abnormalities in the absence of any improvement in the serum biochemical profile. Treatment of either mouse model with the CYP24 inhibitor CTA102 also attenuated skeletal abnormalities. In the accompanying Commentary, Valentin David and Myles Wolf discuss how these findings indicate that pharmacological inhibition of CYP24 could be used as a therapeutic adjuvant in the treatment of FGF23-mediated renal phosphate wasting disorders.

Related Commentary
Pruning the ricket thicket
Valentin David and Myles Wolf
http://jci.me/85005

Placental growth factor promotes airway hyperresponsiveness in sickle cell disease

Over half of children with sickle cell disease (SCD) exhibit airway hyperresponsiveness (AHR), even in the absence of asthma. Because placental growth factor (PIGF) is elevated in the plasma of patients with SCD and contributes to inflammation, Marthe-Sandrine Eiymo Mwa Mpollo and colleagues examined the role of PIGF in SCD-associated AHR. Loss of PlGF in mice blunted AHR and inflammation (see the accompanying image) in response to house dust mite (HDM) allergen and decreased goblet cell metaplasia and eosinophil recruitment compared with WT mice. Mechanistically, PIGF upregulates the Th2 cytokine IL-13 via STAT6 and activates a leukotriene-dependent pathway that drives AHR. Moreover, SCD mice exhibited increased AHR and elevated leukotriene levels that were attenuated by administration of an anti-PIGF antibody or zileuton, an inhibitor of the leukotriene generator 5-lipoxygenase.

Related Commentary

Placenta growth factor augments airway hyperresponsiveness via leukotrienes and IL-13
Marthe-Sandrine Eiymo Mwa Mpollo, Eric B. Brandt, Shiva Kumar Shannukhappa, Paritha I. Arumugam, Swati Tiwari, Anastasia Loberg, Devin Pillis, Tilat Rizvi, Mark Lindsey, Bart Jonck, Peter Carmeliet, Vijay K. Kalra, Timothy D. Le Cras, Nancy Rotner, Marsha Wills-Karp, Gurjit K. Khurana Hershey, and Punam Malik
http://jci.me/77250
CXCR5/CXCL13 signaling mediates neuropathic pain in mice

Recent studies have implicated chemokine signaling in microglial activation and neuropathic pain. Bao-Chun Jiang and colleagues found that the chemokine CXCL13 was persistently upregulated in spinal cord neurons after spinal nerve ligation (SNL), a murine model of neuropathic pain. Intrathecal injection of CXCL13 induced astrocyte activation (see the accompanying image) and pain hypersensitivity via the chemokine receptor CXCR5, which is also upregulated after SNL, and the MAPK ERK. Conversely, shRNA-mediated inhibition of CXCL13 or deletion of Cxcr5 abrogated SNL-induced neuropathic pain. Additionally, CXCL13 colocalized with miR-186-5p, which was downregulated after SNL in the spinal cord. Overexpression of miR-186-5p decreased CXCL13 expression and attenuated neuropathic pain. These findings suggest that CXCL13, CXCR5, and miR-186-5p may be suitable therapeutic targets for neuropathic pain.

CXCL13 drives spinal astrocyte activation and neuropathic pain via CXCR5

Bao-Chun Jiang, De-Li Cao, Xin Zhang, Zhi-Jun Zhang, Li-Na He, Chun-Hua Li, Wen-Wen Zhang, Xiao-Bo Wu, Temugin Berta, Ru-Rong Ji, and Yong-Jing Gao

http://jci.me/81950

Translating a rodent behavioral assay for humans

Behavioral assays for the assessment of neurological and cognitive phenotypes are a cornerstone of research using rodent models of Alzheimer’s disease (AD); however, clinical trials based on results from these models have been largely unsuccessful. Katherine Possin and colleagues developed a virtual version of the most frequently used behavioral assay of spatial learning and memory in rodents, the Morris water maze (MWM), and tested it in humans. They compared the sensitivity of the traditional assay in mice expressing human amyloid precursor protein (hAPP) and patients with mild cognitive impairments due to AD. Possin and colleagues found that the patients and hAPP mice exhibited similar deficits in learning and remembering a target location, but only the hAPP mice showed deficits in procedural learning. In the accompanying Commentary, Kerin Higa, Jared Young, and Mark Geyer discuss how these findings suggest strategies to make the MWM more relevant to learning and memory deficits in humans.

Cross-species translation of the Morris maze for Alzheimer’s disease

Katherine L. Possin, Pascal E. Sanchez, Clifford Anderson-Bergman, Roland Fernandez, Geoffrey A. Kerchner, Erica T. Johnson, Allyson Davis, Iris Lo, Nicholas T. Bott, Thomas Kiely, Michelle C. Fenney, Bruce L. Miller, Joel H. Kramer, and Steven Finkbeiner

http://jci.me/78464

Related Commentary

Wet or dry: translatable “water mazes” for mice and humans

Kerin K. Higa, Jared W. Young, and Mark A. Geyer

http://jci.me/86071
The development of combination antiretroviral therapy in the mid-1990s initially raised hopes that HIV was a curable disease; however, further studies revealed that the virus persists, even in patients with undetectable levels of HIV in their plasma. Resting CD4+ T cells harbor stably integrated viral genomes that can produce infectious virus following T cell activation. Importantly, treatment interruption leads to a rapid recrudescence of infection from this latent reservoir, usually within two to three weeks. Several distinct areas of HIV research are now focused on the development of strategies to prevent the latent reservoir from replicating or to eliminate it entirely. Reviews in this series detail progress in our understanding of the molecular and cellular mechanisms of viral latency, efforts to accurately assess the size and composition of the latent viral reservoir, the characterization and development of HIV-targeted broadly neutralizing antibodies and cytolytic T lymphocytes, and animal models for the study of HIV latency and therapeutic strategies.

**Recent developments in the effort to cure HIV infection: going beyond N = 1**
Janet D. Siliciano and Robert F. Siliciano

Dr. Robert Siliciano is a Howard Hughes Medical Institute investigator and Professor of Medicine at the Johns Hopkins University School of Medicine, with a joint appointment in the Department of Molecular Biology and Genetics. In 1995, Dr. Siliciano’s group provided the first demonstration that latently infected CD4+ T cells were present in patients with HIV-1 infection. His laboratory has gone on to characterize the different forms of HIV that persist in patients on antiretroviral therapy (ART) and to explore potential strategies for eliminating the virus, including the evaluation of drugs that target the latent reservoir and the development of assays that can be used to monitor the elimination of this reservoir.
HIV persistence, integration, and clonal expansion

HIV cure will necessitate the use of strategies that eliminate all copies of the virus from host cells; however, for such strategies to be successful, it will be necessary to understand exactly how HIV persists in the host before and during antiretroviral therapy (ART). Integration of proviruses into the genome of host cells is a common feature of retroviruses, including HIV. Recent technological advances have allowed the characterization of proviruses and the host genes into which they integrate. Frank Maldarelli describes HIV populations prior to and following the introduction of ART, the central role of HIV integration in long-term persistence, the evidence for clonal expansion of HIV-infected cells, and current concepts regarding the role of clonal expansion in the persistence of replication-competent HIV.

The role of HIV integration in viral persistence: no more whistling past the proviral graveyard
Frank Maldarelli  http://jci.me/80564

Methods to measure the HIV latent reservoir

The HIV latent reservoir is composed of infected cells that contain a viral genome in a dormant state from which virus replication can be induced. The ability to accurately measure the number of latently infected cells will be critical to assessing the effects of therapeutic strategies for eliminating the latent viral reservoir. Marta Massanella and Douglas Richman review the attributes and limitations of the methods that are currently being employed to measure the latent reservoir, including PCR-based assays and quantitative viral outgrowth assays (QVOA). Characterization of these assays will require standardization of the procedures used in different laboratories and rigorous evaluation of sensitivity, specificity, and reproducibility, as well as comparisons to clinical results.

Measuring the latent reservoir in vivo
Marta Massanella and Douglas D. Richman  http://jci.me/80567

Murine models of HIV infection

Despite the ability of modern antiretroviral therapy (ART) to suppress virus in the peripheral blood, HIV persists in patients indefinitely, and treatment interruption results in a rapid rebound of plasma viremia. The viral reservoir is likely to reside in cells and tissues such as the brain that are not easily accessible for analysis; therefore, animal models of HIV infection are required for the investigation of HIV persistence as well as the testing of strategies to eradicate the virus. J. Victor Garcia examines the utility of animal models for the investigation of HIV persistence and eradication strategies, focusing on recent humanized mouse models (see the accompanying image). Humanized mouse models can be used for the study of different types of viral infection, the analysis of latency and persistence in HIV-targeted human cell types in the periphery and within tissues, and the in vivo evaluation of new and established ART combinations, as well as novel shock-and-kill strategies.

In vivo platforms for analysis of HIV persistence and eradication
J. Victor Garcia  http://jci.me/80562
Hematopoietic stem cell transplantation for HIV cure: challenges and perspectives

Because antiretroviral therapy cannot completely eliminate HIV, patients can never be fully cured and must remain on therapy for the rest of their lives. A single HIV-infected patient with refractory lymphoma achieved apparent cure following hematopoietic stem cell transplantation (HSCT) from an allogeneic donor homozygous for the ccr5Δ32 mutation, which prevents infection with CCR5-tropic HIV strains. Daniel Kuritzkes reviews the experience with HSCT in HIV-infected patients to date and surveys the ongoing work in this field. Attempts to replicate the apparent cure of HIV-1 infection by HSCT have failed thus far, indicating that transplantation with CCR5-deficient cells is necessary but possibly not sufficient for eradication of the virus. Kuritzkes also discusses the potential of using genetically modified hematopoietic stem cells to cure HIV. Importantly, there are concerns regarding the safety of subjecting otherwise healthy HIV-infected individuals to HSCT.

Hematopoietic stem cell transplantation for HIV cure
Daniel R. Kuritzkes  http://jci.me/80563

Search and destroy: helping CD8+ T cells eliminate HIV

HIV infection elicits a vigorous HIV-specific response; however, the immune system is unable to eliminate infected cells. Studies using pharmacological strategies to drive the expression of virus in latently infected cells have indicated that infected cells do not die by viral cytopathic effects and will need to be eliminated by HIV-specific cytotoxic T lymphocytes (CTLs). Importantly, this anti-HIV response will need to be more potent than the response elicited by a naturally occurring infection. R. Brad Jones and Bruce Walker discuss the factors that determine the ability of CTLs to recognize infected cells and the barriers to CTL-mediated clearance of HIV-infected cells, including viral immune escape, T cell exhaustion and dysfunction, compartmentalization of CTLs and viral reservoirs, and HIV latency, as well as therapeutic strategies to overcome these barriers (see the accompanying image).

HIV-specific CD8+ T cells and HIV eradication
R. Brad Jones and Bruce D. Walker  http://jci.me/80566

Understanding HIV gene expression and latency

Resting CD4+ T cells as well as potentially other cells and tissues within the body harbor latent proviruses that are stably integrated into the genome. The goal of shock-and-kill strategies is to force latently infected cells to express virus so that they can be cleared by the immune system. Understanding the basic mechanisms that govern HIV gene expression will aid in the development of methods to induce viral expression. Daniele Cary, Koh Fujinaga, and Matija Peterlin describe the pathways that mediate HIV gene expression (see the accompanying image), including the mechanisms that prevent expression in latent cells. Additionally, they identify critical cellular and viral factors that may be suitable therapeutic targets for inducing viral expression while preventing T cell activation.

Molecular mechanisms of HIV latency
Daniele C. Cary, Koh Fujinaga, and B. Matija Peterlin  http://jci.me/80565
Tubular Dickkopf-3 promotes the development of renal atrophy and fibrosis

Loss of the Wnt pathway modulator Dickkopf-3 (DKK3) protects mice from kidney fibrosis, and elevated DKK3 correlates with interstitial fibrosis in patients.


http://jci.me/84916

Interaction of β1-adrenergic receptor with RAGE mediates cardiomyopathy via CaMKII signaling

The β1-adrenergic receptor and danger signal pattern recognition receptor RAGE mediate myocardial cell death in a functionally dependent manner.

Weizhong Zhu, Sharon Tsang, David M. Browe, Anthony Y.H. Woo, Ying Huang, Chanjuan Xu, Jian-Feng Liu, Fengxiang Lv, Yan Zhang, and Rui-ping Xiao

http://jci.me/84969

Blocking MHC class II on human endothelium mitigates acute rejection

In a humanized mouse model, endothelial cell MHC class II activates CD4+ T effector memory cells and promotes vascular allograft rejection.

Parwiz Abrahimi, Lingfeng Qin, William G. Chang, Alfred L.M. Bothwell, George Tellides, W. Mark Saltzman, and Jordan S. Pober

http://jci.me/85293

Relationships among injury, fibrosis, and time in human kidney transplants

Transcriptome analysis of human kidney transplant biopsies suggests that fibrosis reflects an adaptive response to injury.

Jeffery M. Venner, Konrad S. Famulski, Jeff Reeve, Jessica Chang, and Philip F. Halloran

http://jci.me/85323

More information: http://jci.me/insinf or editors@insight.jci.org