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Louisiana State University
Health Sciences Center - Shreveport

Vice Chancellor for Research

The LSU Health Sciences Center in Shreveport, LA is seeking candidates for the role of Vice Chancellor for Research. The individual selected for this position will provide executive leadership for research administration and planning, and will work with fellow leaders to strengthen the campus research enterprise and infrastructure for an innovative and multi-disciplinary research program across North Louisiana.

The Vice Chancellor for Research will lead the institution in all areas of research. The Vice Chancellor will represent the campus in matters related to research including federal and state agencies, other research institutions and the local community. A priority for the incumbent will be to facilitate translational research opportunities. Additionally, the Vice Chancellor will be the designated Institutional Official responsible for research across the organization.

The institution’s 436 bed University Hospital serves an urban and rural population of approximately 2.5 million, encompassing 25,000 square miles in Louisiana, East Texas, and Southwestern Arkansas. The resources for basic and clinical research are excellent. We have a long history of successful research collaboration between the basic science and clinical departments. The Virginia Shehee Biomedical Research Institute is ~160,000 total square feet and includes wet lab and staffed core facilities, such as for cellular imaging, DNA array analysis, and mass spectroscopy-proteomics. For more information on this opportunity at LSUHSC please visit us at http://www.lsuhschsreveport.edu/VCWorking

Prospectus

Successful candidates must be an MD/PhD or MD with an outstanding record of scholarly achievement, including a history of independent federal research funding, serving as a principal investigator and having administrative experience relevant to clinical and basic research. Requirements include an understanding of the diverse forms of research and scholarship conducted at a comprehensive research university, and an informed perspective about federally sponsored programs, intellectual property, technology transfer and commercialization in the university setting.

The search is being led by Glenn Mills, MD, FACP, Professor of Medicine, Chief, Section of Hematology and Oncology and Director, Feist-Weiller Cancer Center. Interested candidates may submit curriculum vitae via email at ShvFacultyRecruiting@lsuhsc.edu

Materials that cannot be submitted electronically may be mailed to: Vice Chancellor for Research Recruitment, Human Resource Management, 1501 Kings Highway, Shreveport, LA 71103.

LSU Health Shreveport respects diversity in the workplace and is an Equal Opportunity Employer.

Associate Dean for Clinical and Transitional Research

UNIVERSITY OF WISCONSIN-MADISON — The University of Wisconsin, established in 1848 and considered one of the outstanding public research universities in the United States, invites applications and nominations for a new position as associate dean for clinical and translational research in the UW School Medicine and Public Health (SMPH). The associate dean will be embedded in the UW Institute for Clinical and Translational Research (ICTR), which in 2012 began its second five-year project period, supported by a $41.5 million NIH Clinical and Translational Science Award (CTSA) grant.

The associate dean for clinical and translational research will focus their effort on ICTR, initially as a Co-PI on the CTSA grant, collaborating with the current PI and his/her seven-person leadership team to oversee and contribute to growth of the program. The UW ICTR also has $1.5 million of additional NIH funding and local funding of $8 million per year for its enterprise.

UW-Madison is a major land-grant university committed to excellence in teaching, research and public service, with a robust health sciences community and a campus environment that facilitates cross disciplinary collaborative research, revenues of $2.7 billion, a student body of approximately 42,000, and faculty/staff of approximately 16,000. The School of Medicine and Public Health is renowned for award winning research that covers the entire spectrum of basic, clinical, population, and translational investigation, as well as its outreach mission to Wisconsin in the public health, policy, and health services areas.

ICTR, under its NIH CTSA grant, is a partnership of four UW health science schools (Schools of Medicine and Public Health, Pharmacy, Nursing, Veterinary Medicine) and the College of Engineering, and a successful statewide partnership with the renowned Marshfield Clinic and its research foundation, home to an award-winning personalized medicine program.

The associate dean will report to the SMPH senior associate dean for clinical and translational research, who, as CTSA PI, reports to the Provost and the SMPH Dean. The new associate dean will reside in the ICTR suite that occupies one-third of the 6th floor Health Sciences Learning Center, which also houses the SMPH dean’s offices. In addition, also in the HSLC, the ICTR has a client services center, along with a Health Equity Collaborative Center Core, funded by an NIH P60 grant.

Candidates will be evaluated on the following professional and personal characteristics:

• commitment to maintain and extend the scholarly values, academic and outreach programs, and mission of the school;
• record of successful visionary and collaborative leadership;
• strong administrative, communication, and financial management skills;
• commitment and ability to work with faculty, staff, and students;
• commitment and ability to work with the leadership of an academic group practice, teaching hospitals, and other vital academic health partner organizations; understanding and appreciation of the diverse missions and constituencies of a major public research university;
• commitment to advocate and pursue funding from public and private sources;
• ability to work with external constituencies, including state and federal government;
• demonstrated commitment to the diversity of students, faculty and staff, and to advancing an inclusive diverse climate that stimulates excellence.

Under the NIH CTSA requirements, the CTSA Co-PI must be an established clinician scientist, who has NIH funding (ROI) for independent research pursuits. This new UW associate dean will have a commitment of six months effort to the CTSA grant and daily involvement with the activities of the CTSA. The Co-PI must meet all eligibility requirements for this CTSA position, which includes a record of scholarship, teaching, and service that qualifies him/her for tenure at the level of full professor at UW-Madison.

Electronic applications and nominations must be received by 13 December 2013 to ensure consideration. Later applications and nominations may also be considered. The committee particularly encourages applications and nominations of women and persons of underrepresented groups. Applicants should include a current resume or curriculum vitae and a comprehensive cover letter that addresses how their strengths and experience match the qualifications for the position, and what they see as challenges and opportunities of the position, as well as the names, addresses, e-mails, and telephone numbers of five references. Candidates will be informed of references are contacted.

Please note that in accordance with Wisconsin statutes, the names of nominees and applicants who explicitly request confidentiality will not be made public. However, the university is required to release the names of the finalists. Submit applications and nominations electronically to the SMPH Research Dean Search and Screen Committee at:

Paulette Sacksteder, Administrative Director
UW-Madison ICTR, 4241 HSLC
750 Highland Avenue, Madison, WI 53705

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**Featured Editor**

Douglas A. Marchuk, Ph.D., Associate Editor, is Professor in and Vice Chair of the Department of Molecular Genetics and Microbiology and Director of the Duke University Program in Genetics and Genomics. His primary research interest is the genetics of cardiovascular disease. His laboratory has identified the causative genes for a number of Mendelian disorders of vascular dysplasia, including hereditary hemorrhagic telangiectasia and cerebral cavernous malformations. Using murine models of these phenotypes, he continues to investigate the pathobiology and potential therapies for these diseases. In addition, Dr. Marchuk studies genetic modifiers of cardiovascular disease using quantitative trait locus mapping in established murine models of disease.

**Publication highlights**


Research articles in the current issue of the JCI

Cardiology

**Inhibition of Coxsackievirus-associated dystrophin cleavage prevents cardiomyopathy**
Byung-Kwan Lim, Angela K. Peter, Dingding Xiong, Anna Narezkina, Aaron Yung, Nancy D. Dalton, Kyung-Kuk Hwang, Toshitaka Yajima, Ju Chen, and Kirk U. Knowlton  
[http://jci.me/66271](http://jci.me/66271)

**Insulin receptor substrate signaling suppresses neonatal autophagy in the heart**
Christian Riehle, Adam R. Wende, Sandra Sena, Karla Maria Pires, Renata Oliveira Pereira, Yi Zhu, Heiko Bugger, Deborah Frank, Jack Bevins, Dong Chen, Cynthia N. Perry, Xiaocheng C. Dong, Steven Valdez, Monika Rech, Xiaoming Sheng, Bart C. Weimer, Roberta A. Gottlieb, Morris F. White, and E. Dale Abel  
[http://jci.me/71171](http://jci.me/71171)

**Enhanced autophagy ameliorates cardiac proteinopathy**
Md. Shenuarin Bhuiyan, J. Scott Pattison, Hanna Osinska, Jeanne James, James Gulick, Patrick M. McLendon, Joseph A. Hill, Junichi Sadoshima, and Jeffrey Robbins  
[http://jci.me/70877](http://jci.me/70877)

**Apelin is a positive regulator of ACE2 in failing hearts**
Teruki Sato, Takashi Suzuki, Hiroyuki Watanabe, Ayumi Kadowaki, Akiyoshi Fukamizu, Peter P. Liu, Akinori Kimura, Hiroshi Ito, Josef M. Penninger, Yumiko Imai, and Keiji Kuba  
[http://jci.me/69608](http://jci.me/69608)

Dermatology

**Topical hypochlorite ameliorates NF-κB–mediated skin diseases in mice**
Thomas H. Leung, Lillian F. Zhang, Jing Wang, Shoucheng Ning, Susan J. Knox, and Seung K. Kim  
[http://jci.me/70895](http://jci.me/70895)

Gastroenterology

**Retinoblastoma protein prevents enteric nervous system defects and intestinal pseudo-obstruction**
[http://jci.me/67653](http://jci.me/67653)

Hematology

**von Willebrand factor mutation promotes thrombocytopenia by inhibiting integrin αIIbβ3**
Caterina Casari, Eliane Berrou, Marilyne Lebret, Frédéric Adam, Alexandre Kauskot, Régis Bobe, Céline Desconclois, Edith Fressinaud, Olivier D. Christophe, Peter J. Lenting, Jean-Philippe Rosa, Cécile V. Denis, and Marijke Bryckaert  
[http://jci.me/69458](http://jci.me/69458)

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**TSC1 regulates the balance between effector and regulatory T cells**
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http://jci.org/impact/december2013/3

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**Human Treg responses allow sustained recombinant adeno-associated virus–mediated transgene expression**
http://jci.org/impact/december2013/3

*With related Commentary by Kai Yang and Hongbo Chi*  
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**Protein microarray analysis reveals BAFF-binding autoantibodies in systemic lupus erythematosus**
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**ADCK4 mutations promote steroid-resistant nephrotic syndrome through CoQ10$_{10}$ biosynthesis disruption**
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**CX$_3$CR1-dependent renal macrophage survival promotes Candida control and host survival**
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Systems pharmacology identifies drug targets for Stargardt disease–associated retinal degeneration
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AKT activation promotes PTEN hamartoma tumor syndrome–associated cataract development

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Histone deacetylase 6–mediated selective autophagy regulates COPD-associated cilia dysfunction

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Transmembrane protein ESDN promotes endothelial VEGF signaling and regulates angiogenesis
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Mice generated by in vitro fertilization exhibit vascular dysfunction and shortened life span
Emrush Rexhaj, Ariane Paoloni-Giacobino, Stefano F. Rimoldi, Daniel G. Fuster, Manuel Andereg, Emmanuel Somm, Elisa Bouillet, Yves Alleman, Claudio Sartori, and Urs Scherrer  http://jci.me/68943
The enteric nervous system controls critical aspects of intestinal motility, and disruption of this network may contribute to serious intestinal diseases, such as chronic intestinal pseudo-obstruction. In this month’s issue, Ming Fu and colleagues uncovered an unexpected function for the cell cycle regulator retinoblastoma protein (RB1) in enteric nervous system development. Using knockout mice with targeted deletion of Rb1 in the neural crest lineage, the research team found that young mice succumbed to intestinal obstruction with profound defects in the enteric nervous system and abnormal small bowel contractility. Striking abnormalities were observed in neurons that produce nitric oxide (NO), a key neurotransmitter for inhibitory motor neurons that controls intestinal motility, but other myenteric neuron subtypes evaluated appeared unaffected. NO-producing enteric neurons had abnormally large nuclei due to multiple rounds of DNA replication without cell division, known as endoreplication. In vitro studies suggested that the phenotype of irregularly shaped nuclei found in NO-producing neurons was similar to defects seen in progeria, an early-onset aging disorder linked to RB1 dysfunction. The accompanying image shows enteric neurons stained for HuC/D (red), including enlarged NO-producing neurons, as well as neurites stained for TuJ1 (green) and DNA (DRAQ5, blue) in the myenteric plexus from the distal small bowel of an Rb1-knockout mouse.
mTOR regulators strike a balance in T cell immune responses

The differentiation of naive T cells is critical to the development of appropriate immune responses. mTOR signaling is an important mediator of T cell differentiation, and fine-tuning of this pathway substantially impacts the balance between T cell–mediated immunity and tolerance. To determine how mTOR signaling impacts T cell differentiation under normal and inflammatory conditions, Yoon Park and colleagues used mice with conditional loss of tuberous sclerosis complex 1 (TSC1), an inhibitor of mTORC1. They report that loss of Tsc1 in T cells augmented the differentiation of Th1 and Th17 cells, which enhanced inflammation in a murine model of colitis. The accompanying image shows WT (left) and Tsc1-deficient (right) colon. Loss of Tsc1 in Tregs impaired the ability of these cells to suppress inflammation and was associated with the acquisition of effector T cell–like phenotypes, further exacerbating inflammatory immune responses. In an accompanying Commentary, Kai Yang and Hongbo Chi discuss how signals that sustain or block TSC1 must be tightly regulated to control T cell composition and strike the correct balance between immunity and tolerance.

TSC1 regulates the balance between effector and regulatory T cells

Yoon Park, Hyung-Seung Jin, Justine Lopez, Chris Elly, Gisen Kim, Masako Murai, Mitchell Kronenberg, and Yun-Cai Liu  http://jci.me/69751

Related Commentary
Tuning mTOR activity for immune balance
Kai Yang and Hongbo Chi  http://jci.me/73202

Intravital tracking of anti-CD20 antibody therapy reveals B cell depletion mechanisms

Therapy using anti-CD20 antibodies, such as rituximab, mediates B cell depletion and has been used to successfully treat autoimmune diseases and B cell malignancies. It is unclear, however, exactly how these antibodies behave in vivo. Fabricio Montalvao and colleagues used intravital 2-photon imaging to track the effects of anti-CD20 antibodies in mice. They found that the liver sinusoids represent a major site of B cell depletion, which was mediated by Kupffer cells (KCs). Moreover, KCs depleted B cells in a lymphoma model. These results identify a primary mechanism by which anti-CD20 antibodies deplete B cells and indicate that intravital imaging could be used to optimize anti–B cell therapies.

The mechanism of anti-CD20–mediated B cell depletion revealed by intravital imaging
Fabricio Montalvao, Zacarias Garcia, Susanna Celli, Béatrice Breat, Jacques Deguine, Nico Van Rooijen, and Philippe Bousson  http://jci.me/70972

A high-throughput platform for identification of serum factor–reactive antibodies

Serum factor–reactive antibodies, which target the circulating cytokines, chemokines, and other factors that regulate the immune system, are a characteristic of multiple immune disorders. Many of these antibodies exacerbate disease pathology, and identification and characterization of the targeted serum factors will help contribute to our understanding of these diseases. Jordan Price and colleagues constructed a multiplex protein microarray to detect serum factor antibodies in patient serum. Using this platform, Price and colleagues screened the serum of SLE patients for known and novel antibodies and identified IgG autoantibodies that recognize B cell–activating factor (BAFF) and additional soluble factors. These antibodies neutralized BAFF activity in vitro. Furthermore, elevated levels of BAFF antibodies were associated with more severe disease. In an accompanying Commentary, Stefanie Sarantopoulos and Maureen Su discuss how these findings alter our understanding of SLE pathogenesis.

Protein microarray analysis reveals BAFF-binding autoantibodies in systemic lupus erythematosus


Related Commentary
BAFF-ling autoantibodies
Stefanie Sarantopoulos and Maureen A. Su  http://jci.me/73166
Loss of PTEN alters ion exchange activity in the lens

PTEN hamartoma tumor syndrome (PHTS) is a highly variable disorder caused by mutations in PTEN that is frequently accompanied by cataracts. Caterina Sellitto and colleagues used mice with lens-specific loss of Pten to determine whether PTEN contributes directly to this phenotype. They found that mice with Pten-deficient lenses developed cataracts (see accompanying image) and exhibited significantly reduced Na+/K+ exchanger activity, leading to increased intracellular sodium concentrations and hydrostatic pressure. Further investigation of the signaling pathway revealed that loss of Pten increased activation of AKT, which downregulated Na+/K+ exchanger activity. These data identify a previously unappreciated role for PTEN/AKT in ion transport regulation and shed light on the cellular alterations that underlie PHTS-associated cataracts.

AKT activation promotes PTEN hamartoma tumor syndrome–associated cataract development


COPD-associated ciliopathy blocked by histone deacetylase inhibition

Chronic obstructive pulmonary disease (COPD) is characterized by epithelial cell dysfunction, shortening of motile cilia, disrupted mucus clearance, aberrant airway inflammation in response to irritants, and decreased lung function. The disruptions in mucus clearance have been attributed to the shortening of motile cilia after irritant exposure. The accompanying image shows decreased cilia in the airways of mice exposed to cigarette smoke (CS).

Hilaire Lam, Suzanne Cloonan, and colleagues examined the contribution of autophagy to cilia shortening (ciliophagy) in COPD using transgenic mice with impaired autophagy (Becn1+/– or Map1lc3B–/–). Unlike WT mice, autophagy-impaired mice did not exhibit cilia shortening in response to CS exposure. Similarly, mice lacking the X chromosome copy of Hdac6, a histone deacetylase that contributes to autophagosome-lysosome fusion, exhibited reduced autophagy but did not display CS-induced cilia shortening or disrupted mucus clearance. These data suggest that disruption of ciliophagy could serve as a therapeutic strategy in the treatment of COPD.

Histone deacetylase 6–mediated selective autophagy regulates COPD-associated cilia dysfunction


Mice conceived by in vitro fertilization exhibit vascular dysfunction

Recent epidemiological data suggest that the use of in vitro fertilization (IVF) is associated with vascular dysfunction in the resulting offspring. Emrush Rexhaj and colleagues developed a murine model of IVF to examine the long-term consequences and molecular mechanisms of IVF’s effects on the vasculature. They found that mice conceived by IVF displayed endothelial dysfunction and arterial hypertension and had shorter life spans when fed a high-fat diet. These physiological alterations were associated with changes in promoter methylation of eNOS, a known regulator of endothelial function. Further, IVF-conceived male mice transmitted this dysfunction to their progeny through altered genetic imprinting in the aorta. Taken together, these data suggest that, in mice, IVF induces epigenetic changes that can lead to premature cardiovascular morbidity and mortality in the offspring.

Mice generated by in vitro fertilization exhibit vascular dysfunction and shortened life span

Ermush Rexhaj, Ariane Paoloni-Giacobino, Stefano F. Rimoldi, Daniel G. Fuster, Manuel Anderegg, Emmanuel Somm, Elisa Bouillet, Yves Alleman, Claudio Sartori, and Urs Scherrer
Mapping the neural circuits mediating negative affect

Mapping the activity of functional circuits within the brain is a long-held goal of neuroscience. Yasmin Hurd and colleagues used specially engineered receptor constructs known as designer receptors exclusively activated by designer drugs (DREADDs), in conjunction with \[^{18}F\]fluorodeoxyglucose \(\mu\)PET, to perform DREADD-assisted metabolic mapping (DREAMM) in the brain. DREAMM was then used to explore the functional circuits that mediate negative affect and opiate addiction in rats. Chronic negative emotional states are a characteristic of both major depressive disorder (MDD) and recurrent drug abuse. Abnormal prodynorphin (PDYN) signaling in the amygdala has previously been implicated in both conditions. Hurd and colleagues found that PDYN mRNA was decreased in the periamygdaloid cortex (PAC) of two postmortem heroin abuse cohorts as well as subjects with MDD. Similarly, Pdyn mRNA was reduced in rats with chronic heroin self-administration. Using DREAMM, the authors demonstrated that inhibition of PDYN-expressing neurons in the PAC increased activity in the amygdala (see accompanying image), leading to neural stress and depression-related phenotypes in rats. These findings identify a neuronal circuit involved in negative affect and opiate addiction and serve as a proof of principle for a technique for mapping neuronal circuits in vivo.

Related research

**Impaired periamygdaloid-cortex prodynorphin is characteristic of opiate addiction and depression**

**Whole-brain circuit dissection in free-moving animals reveals cell-specific mesocorticolimbic networks**

Finding a rhythm in neurodegeneration

Clock proteins control circadian rhythms at the molecular level. The circadian output from the suprachiasmatic nucleus (SCN) is responsible for synchronizing tissue-specific clocks throughout the body, which impact cellular redox and metabolic pathways. Clock gene dysfunction in peripheral tissues has previously been shown to result in increased oxidative stress and aging. In this issue, Erik Musiek and colleagues demonstrate that brain-specific loss of the clock gene \textit{Bmal1} caused degeneration of synaptic nerve terminals and age-dependent increases in astrocyte activation in the cortex and hippocampus of mice, a phenomenon commonly associated with neurodegenerative disease. The accompanying image shows expression of the astrocyte marker GFAP in the cortex of 6-month-old WT (top) and \textit{Bmal1}-deficient mice (bottom). Moreover, loss of \textit{Bmal1} promoted neuronal cell death and increased oxidative stress in cultured neurons. Colleen McClung discusses how these findings connect impaired clock gene function with neurodegeneration in the accompanying Commentary.

Circadian clock proteins regulate neuronal redox homeostasis and neurodegeneration

Erik S. Musiek, Miranda M. Lim, Guangrui Yang, Adam Q. Bauer, Laura Qi, Yool Lee, Jee Hoon Roh, Xilma Ortiz-Gonzalez, Joshua T. Dearborn, Joseph P. Culver, Erik D. Herzog, John B. Hogenesch, David F. Wozniak, Krikor Dikranian, Benoit I. Giasson, David R. Weaver, David M. Holtzman, and Garret A. FitzGerald  [http://jci.me/70317](http://jci.me/70317)

Related Commentary

**Mind your rhythms: an important role for circadian genes in neuroprotection**
Colleen A. McClung  [http://jci.me/73059](http://jci.me/73059)
New insights into platelet function in type 2B von Willebrand disease

Type 2B von Willebrand disease (VWD-type 2B) is a hereditary coagulation disorder that arises from a gain-of-function mutation in von Willebrand factor (vWF) and is characterized by moderate to severe thrombocytopenia. It is not clear whether impaired platelet function contributes to the bleeding phenotype seen in these patients. Using transgenic mice that express VWD-type 2B-associated mutant vWF and platelets from a patient with the same VWD-type 2B mutation, Caterina Casari and colleagues demonstrated that this mutation leads to impaired aggregation, secretion, and spreading of platelets. These defects were attributable to inhibition of integrin αIIbβ3 activation and subsequent thrombus growth, which was observed in both the mutant mice and the patient. These studies indicate that the VWD-type 2B mutation causes defective platelet function that likely contributes to bleeding defects. In the accompanying Commentary, Jerry Ware discusses how these findings explain the mechanism behind a gain-of-function mutation that was identified more than 30 years ago.

von Willebrand factor mutation promotes thrombocytopenia by inhibiting integrin αIIbβ3
Caterina Casari, Eléonore Berrou, Marilyne Lebret, Frédéric Adam, Alexandre Kauskat, Régis Bobe, Céline Desconclos, Edith Fressinaud, Olivier D. Christophe, Peter J. Lenting, Jean-Philippe Roso, Cécile V. Denis, and Marijke Bryckaert
http://jci.me/69458

Related Commentary
Thrombocytopenia and type 2B von Willebrand disease
Jerry Ware http://jci.me/73169

Radioresistance in EBV-associated nasopharyngeal carcinoma is mediated by LIF

Radioresistance in EBV-associated nasopharyngeal carcinoma (NPC) is mediated by leukemia inhibitory factor (LIF). Shu-Chen Liu and colleagues found that higher serum levels of LIF were associated with lower incidence of recurrence in NPC patients. The accompanying histology images show LIF expression in normal tissue (top) and a NPC lesion (bottom). At the molecular level, Liu and colleagues found that LIF activates mTORC1/p70S6K signaling to enhance tumor growth. Further, LIF inhibits DNA damage responses, thereby promoting resistance to radiation-induced cell death. Importantly, the effectiveness of radiotherapy could be increased by the administration of LIF or mTOR inhibitors. In an accompanying Commentary, Micah Luftig discusses how these findings alter our understanding of EBV's impact on NPC outcomes.

Related Commentary
Heavy LIFting: tumor promotion and radioresistance in NPC
Micah Luftig http://jci.me/73416

BRAF/PTEN-mutant melanoma is AKT independent

BRAF-targeted agents have emerged as frontline treatments for advanced melanoma; however, the disease remains challenging to treat due to the prevalence of primary or acquired resistance. BRAF mutations are frequently accompanied by silencing of the tumor suppressor PTEN. Victoria Marsh Durban and colleagues investigated the contribution of pathways regulated by PTEN in melanomagenesis. Using genetically engineered mice, Marsh Durban and colleagues demonstrated that modulation of PI3K can substitute for PTEN silencing in BRAFV600E-induced melanoma. However, whereas BRAF/PIK3-mutated melanomas were sensitive to AKT inhibition, BRAFV600E/PTEN-null melanomas were insensitive. Importantly, inhibition of PI3K prevented the growth of BRAFV600E/PTEN-null melanomas, and combination inhibition of BRAF and PI3K more effectively induced melanoma regression than inhibition of either pathway alone. These findings establish PI3K signaling as a critical contributor to the genesis and maintenance of melanoma and suggest that combined inhibition of BRAF and PI3K may be an effective therapeutic approach against BRAFV600E/PTEN-null melanomas.

Differential AKT dependency displayed by mouse models of BRAFV600E-initiated melanoma
Victoria Marsh Durban, Marian M. Deuker, Marcus W. Bosenberg, Wayne Phillips, and Martin McMahon http://jci.me/69619
**Defects in CoQ<sub>10</sub> biosynthesis contribute to steroid-resistant nephrotic syndrome**

Steroid-resistant nephrotic syndrome (SRNS) is the second most common cause of end-stage kidney disease. Shazia Ashraf, Heon Yung Gee, and colleagues used homozygosity mapping and whole-exome resequencing to identify mutations that cause SRNS. These studies revealed biallelic mutations in **ADCK4**, which encodes an enzyme that participates in the biosynthesis of coenzyme Q<sub>10</sub> (CoQ<sub>10</sub>) and is expressed in glomerular podocytes. The mutation resulted in the expression of a truncated form of **ADCK4**. Knockdown of **adck4** in zebrafish recapitulated the nephrotic syndrome (see accompanying image) and resulted in reduced CoQ<sub>10</sub> levels and decreased mitochondrial respiratory activity. Knockdown in cultured human podocytes reduced cellular migration, which could be reversed by supplementation of CoQ<sub>10</sub> or addition of murine **ADCK4**. In the accompanying Commentary, Laura Malaga-Dieguez and Katalin Susztak discuss the potential of CoQ<sub>10</sub> supplementation in the treatment of SRNS.

**ADCK4 mutations promote steroid-resistant nephrotic syndrome through CoQ<sub>10</sub> biosynthesis disruption**


**Chemokine receptor CX<sub>3</sub>CR1 controls *Candida* in the kidney**

Systemic candidiasis is a fungal infection that causes mortality in 30%–40% of patients. Disease outcomes are highly variable and likely related to host-specific risk factors. Using a mouse model of systemic candidiasis, Michail Lionakis and colleagues investigated the role of chemokine receptors that mediate the response of macrophages, which accumulate in tissues infected with *Candida*. They found that macrophages expressing the chemokine receptor CX<sub>3</sub>CR1 play a critical role in the control of fungal proliferation in the kidney. Loss of **Cx3cr1** resulted in increased *Candida*-induced renal failure and mortality and reduced macrophage accumulation in the kidney, which was attributed to decreased macrophage survival. Importantly, Lionakis and colleagues found that the dysfunctional M280 allele of human **CX3CR1** was associated with increased risk of systemic candidiasis in patients.

**CX<sub>3</sub>CR1-dependent renal macrophage survival promotes *Candida* control and host survival**


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**Related Commentary**

ADCK4 “reenergizes” nephrotic syndrome

Laura Malaga-Dieguez and Katalin Susztak

http://jci.me/73168
Insulin signaling regulates postnatal cardiomyocyte autophagy

**Autophagy, a cell survival–promoting process,** is induced by nutrient stress and occurs in the mammalian heart during the perinatal period to help newborns survive starvation until feeding is established. Christian Riehle and colleagues used transgenic mouse models to investigate the mechanisms that suppress autophagy after the establishment of feeding and the resolution of nutrient deficiency. They found that mice with cardiomyocyte-specific deletion of the insulin receptor substrates \(Irs1\) and \(Irs2\) exhibited unrestrained autophagy in the heart, leading to myocyte loss, mitochondrial dysfunction, heart failure, and premature death. The accompanying image shows H&E staining of WT and mutant mouse cardiac tissues 4 weeks after birth. These phenotypes could be attenuated by either genetic suppression of autophagy or activation of mTOR signaling. These findings establish insulin as a critical regulator of cardiomyocyte homeostasis and survival in the postnatal heart.

**Inhibition of Coxsackievirus-associated dystrophin cleavage prevents cardiomyopathy**

Byung-Kwan Lim, Angela K. Peter, Dingding Xiong, Anna Narezkina, Aaron Yung, Nancy D. Dalton, Kyung-Kuk Hwang, Toshitaka Yajima, Ju Chen, and Kirk U. Knowlton

http://jci.me/66271

Enteroviral-mediated cleavage of dystrophin promotes viral cardiomyopathy

**Enteroviruses, such as Coxsackievirus (CV),** are detected in up to 50% of patients with myocarditis and dilated cardiomyopathy. In this issue, Byung-Kwan Lim and colleagues demonstrate that a CV protease contributes to the development of myocarditis through the cleavage of dystrophin, a protein that connects the cytoskeleton of the muscle fiber to the surrounding ECM. Enteroviral protease 2A cleaves both viral and host cell proteins, including dystrophin, but the importance of dystrophin cleavage in viral heart disease and its relation to disruption of the sarcolemma were unknown. Lim and colleagues found that mice carrying a knockin mutation that rendered dystrophin resistant to protease 2A cleavage were resistant to CV-induced cardiomyopathy and exhibited decreased sarcolemmal disruption and viral titers compared with WT mice. Additionally, they showed that inhibition of dystrophin cleavage decreased the cardiomyopathy caused by protease 2A transgenic expression. These results demonstrate that protease 2A–mediated dystrophin cleavage contributes to the development of viral cardiomyopathy by increasing sarcolemmal disruption and viral propagation.

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Adipose tissue, macrophages, and the metabolic syndrome connection

Adiposity is closely correlated with several different physiological parameters, including insulin sensitivity, blood pressure, and serum lipid concentrations as well as obesity-associated diseases, such as type 2 diabetes, stroke, and heart disease. In 2003, Anthony Ferrante and colleagues performed transcriptional profiling of mouse adipose tissue to identify genes associated with adiposity. They found that 30% of the 100 most significantly correlated genes encoded proteins associated with macrophages. Moreover, these cells contribute directly to the elevated levels of inflammatory molecules in adipose tissue. In this issue, Ferrante discusses how these findings have changed our understanding of metabolic syndrome and strengthened the connection between immunology and metabolism.

Macrophages, fat, and the emergence of immunometabolism


Hindsight

Conversations with giants in medicine

Thomas Südhof

In this issue, JCI Editor at Large Ushma Neill interviews Thomas Südhof, the 2013 Nobel Prize Laureate in Physiology or Medicine. Along with James Rothman and Randy Schekman, Südhof elucidated the mechanisms by which cells regulate vesicular transport. Südhof’s research is focused on calcium-regulated neurotransmitter release. Neurotransmitter filled vesicles must dock at a precise location on the membrane and then fuse with the membrane to release the neurotransmitters in response to an action potential–triggered influx of calcium ions. Using biochemical and molecular biology techniques, Südhof identified the proteins that mediate these steps and helped to determine exactly how they are regulated so that neurotransmitters are released on command in a timely and specific manner.

http://jci.me/74014

Review

Advances in selective targeting of serotonin receptors

Serotonin (5-HT) mediates numerous physiological processes in both the brain and the periphery. Therapeutics targeting 5-HT receptors are used in many different diseases, including metabolic and psychiatric disorders. There are fourteen different serotonin receptors expressed throughout the body (see accompanying image). Both the therapeutic actions and side effects of drugs targeting these receptors can frequently be attributed to nonspecific actions on different receptor subtypes. In this issue, Herbert Meltzer and Bryan Roth review the development of drugs that target specific serotonin receptor isoforms and focus specifically on two new drugs, lorcaserin and pimavanserin, which target 5-HT2C and 5-HT2A receptors and have recently been approved for the treatment of obesity and Parkinson’s disease psychosis, respectively.

Lorcaserin and pimavanserin: emerging selectivity of serotonin receptor subtype–targeted drugs

Herbert Y. Meltzer and Bryan L. Roth  http://jci.me/70678
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