

**THIS WEEK****ANALYSIS****COVER STORY****1 Two edges of sickle cell disease**

U.S. and Chinese researchers have shown that inhibiting adenosine-ADORA<sub>2B</sub> signaling could prevent vaso-occlusive crises, a major cause of mortality in sickle cell disease. The team now wants to set up clinical trials with pharma companies.

**TRANSLATIONAL NOTES****4 Circulating translation**

Johnson & Johnson has teamed up with Massachusetts General Hospital to develop new technologies for capturing and characterizing circulating tumor cells. The deal is designed to move the institution's work into product development mode.

**TARGETS & MECHANISMS****5 Bacterial blood brain bypass**

INSERM researchers have identified a mechanism that explains how meningococcus crosses the blood brain barrier. The findings could be used to treat meningococcal sepsis and may have broader applications in delivering therapeutics into the CNS.

**TOOLS****6 New and improved dystrophic mice**

California researchers have developed a mouse model of Duchenne muscular dystrophy that they believe reflects the severity of disease better than current rodent models. The team plans to use the model to identify new combination therapies that both correct the genetic defect and block disease progression.

**THE DISTILLERY****8 This week in therapeutics**

Preventing ischemia and reperfusion injury with benzothiazin-4-one derivatives; reducing colitis using TP5B2 inhibitors; treating vascular inflammation with P2Y6 inhibitors; and more...

**14 This week in techniques**

Mouse models of medulloblastoma; a macroporous ferrogel scaffold for magnetic field-inducible drug or cell delivery; peptide activators of invariant NK T cells; and more...

**INDEXES****16 Company and institution index****16 Target and compound index****Two edges of sickle cell disease**

By *Michael J. Haas, Senior Writer*

A U.S.-China team has shown that inhibiting signaling between adenosine and the adenosine A<sub>2B</sub> receptor in blood could prevent vaso-occlusion and consequent organ damage in sickle cell disease.<sup>1</sup> The researchers already are in talks with companies to run clinical trials of antagonists of the receptor.

Sickle cell disease results from a mutant form of β-hemoglobin (HBB) that is prone to polymerization under hypoxic conditions, resulting in the collapse of red blood cells (RBCs) into a characteristic sickle shape. The sickled RBCs can block blood vessels to cause acute episodes (vaso-occlusive crises) of pain, ischemia, tissue necrosis, organ damage and mortality.

Hydroxyurea is the only approved drug to prevent vaso-occlusive crises. However, the generic chemotherapeutic increases the risks of anemia, life-threatening infections, teratogenicity and cancer.

There are no therapies approved to treat vaso-occlusive crises once they begin, and the precise molecular mechanisms underlying RBC sickling and vaso-occlusion are poorly understood.

To better understand those mechanisms and identify new disease targets, the U.S.-China team looked for molecules in blood that might drive RBC sickling.

First, metabolomic screens showed that adenosine levels were higher in the blood of sickle cell disease patients and mouse models of the disease than in blood from healthy controls.

Next, the team sought to identify which of the four known adenosine receptors interacted with adenosine to promote RBC sickling. They examined RBCs from transgenic mice lacking each receptor in turn to determine that adenosine A<sub>2B</sub> receptor (Adora<sub>2B</sub>)—but none of the other three receptors—was involved in RBC sickling.

To confirm the findings in humans, the team showed that a research-grade ADORA<sub>2B</sub> antagonist, PAB1115, decreased hypoxia-induced sickling in RBCs from sickle cell patients compared with no treatment. A pegylated formulation of adenosine deaminase (PEG-ADA), which is an enzyme that metabolizes adenosine, generated similar results.

In mouse models, PAB1115 or PEG-ADA also decreased RBC sickling compared with no treatment. Treated animals experienced less vaso-occlusion and less damage to the lungs, liver, spleen and kidneys than untreated controls.

Data were reported in *Nature Medicine*.<sup>1</sup>

The team was led by Yang Xia, associate professor of biochemistry

**EDITORIAL****Editor-in-Chief:** Karen Bernstein, Ph.D.**Managing Editor:** Gaspar Taroncher-Oldenburg, Ph.D.**Executive Editor:** Steve Edelson**Senior Editors:** Tracey Baas, Ph.D.; Joanne Kotz, Ph.D.**Writers:** Aaron Bouchie; Chris Cain, Ph.D.; Michael Flanagan; Tim Fulmer, Ph.D.; Michael J. Haas; Stephen Hansen; Kai-Jye Lou; Lauren Martz; Lev Osheroovich, Ph.D.; Steve Usdin**Research Director:** Walter Yang**Research Manager:** Kevin Lehnbeuter**Managing Production Editor:** Ingrid McNamara**Senior Production Editor:** Brandy Cafarella**Production Editor:** Amanda Crawford**Copy Editor:** Nicole DeGennaro**Editorial Assistant:** Mark Zipkin**Design:** Claudia Bentley; Miles DaviesFor inquiries, contact [editorial@scibx.com](mailto:editorial@scibx.com)**PUBLISHING****Publisher:** Peter Collins, Ph.D.**Associate Publishers:** Melanie Brazil, Ph.D.; Eric Pierce**Marketing:** Sara Girard; Rosy Rogers**Technology:** Anthony Barrera; Julia Kulikova**Sales:** Ron Rabinowitz; Tim Tulloch; Geoff Worton**OFFICES****BioCentury Publications, Inc.**San Francisco  
PO Box 1246  
San Carlos, CA 94070-1246  
T: +1 650 595 5333Chadds Ford  
223 Wilmington-West Chester Pike  
Chadds Ford, PA 19317  
T: +1 610 558 1873Chicago  
20 N. Wacker Drive, Suite 1465  
Chicago, IL 60606-2902  
T: +1 312 755 0798Oxford  
287 Banbury Road  
Oxford OX4 7JA  
United Kingdom  
T: +44 (0)18 6551 2184Washington, DC  
2008 Q Street, NW, Suite 100  
Washington, DC 20009  
T: +1 202 462 9582**Nature Publishing Group**New York  
75 Varick Street, 9th Floor  
New York, NY 10013-1917  
T: +1 212 726 9200London  
The Macmillan Building  
4 Crinan Street  
London N1 9XW  
United Kingdom  
T: +44 (0)20 7833 4000Tokyo  
Chiyoda Building 6F  
2-37 Ichigayatamachi  
Shinjuku-ku, Tokyo 162-0843  
Japan  
T: +81 3 3267 8751

SciBX is produced by BioCentury Publications, Inc. and Nature Publishing Group Joint Steering Committee: Karen Bernstein, Ph.D., Chairman & Editor-in-Chief, BioCentury; David Flores, President & CEO, BioCentury; Bennet Weintraub, Finance Director, BioCentury; Steven Inchcoombe, Managing Director, Nature Publishing Group; Peter Collins, Ph.D., Publishing Director, NPG; Christoph Hesselmann, Ph.D., Chief Financial Officer, NPG.

Copyright © 2011 Nature Publishing Group ALL RIGHTS RESERVED.

No part of the SciBX publication or website may be copied, reproduced, retransmitted, disseminated, sold, distributed, published, broadcast, circulated, commercially exploited or used to create derivative works without the written consent of the Publishers. Information provided by the SciBX publication and website is gathered from sources that the Publishers believe are reliable; however, the Publishers do not guarantee the accuracy, completeness, or timeliness of the information, nor do the Publishers make any warranties of any kind regarding the information. The contents of the SciBX publication and website are not intended as investment, business, tax or legal advice, and the Publishers are not responsible for any investment, business, tax or legal opinions cited therein.

and molecular biology at **The University of Texas Health Science Center at Houston**. The group also included researchers from **Central South University**, **The First Xiangya Hospital**, **The Third Xiangya Hospital**, the **University of Colorado Denver** and **Metabolon Inc.**, which performed the metabolomic screens in mouse blood.

Xia told SciBX her team is negotiating with undisclosed drug companies to conduct clinical trials of ADORA<sub>2B</sub> antagonists to prevent vaso-occlusive crises in sickle cell disease.

**ADORable**

“To have a clinically meaningful impact on sickle cell disease, we believe that a good first step is the development of a drug to treat acute vaso-occlusive crisis,” with development of therapies to prevent crisis or treat early stage crisis as longer-term goals, said Rachel King, CEO of **GlycoMimetics Inc.**

John Magnani, the biotech’s CSO and VP, described how an ADORA<sub>2B</sub> antagonist might fit into a sickle cell disease strategy.

“An ADORA<sub>2B</sub> antagonist could prevent sickling and the inflammation that results from it, but once inflammation is full-blown during vaso-occlusive crisis, preventing sickling won’t be effective,” he said. “Our selectin antagonist, GMI-1070, goes after a different hypoxia-induced mechanism than an ADORA<sub>2B</sub> antagonist would. This suggests that the two therapeutic strategies would be compatible” for the treatment and prevention of vaso-occlusive crises, respectively.

GMI-1070 is an injectable glycomimetic inhibitor of E selectin (SELE; CD62E), P selectin (SELP; CD62P) and L selectin (SELL; CD62L) that prevents adhesion between RBCs and circulating monocytes and neutrophils. It is in Phase II testing to treat vaso-occlusive crises in sickle cell disease. The company expects the trial to finish enrolling patients this year.

GlycoMimetics also is exploring second-generation selectin antagonists for chronic use to prevent vaso-occlusive crises.

Joel Linden, a member of the Division in Inflammation Biology at the **La Jolla Institute for Allergy & Immunology (LIAI)**, noted that ADORA<sub>2B</sub> antagonists would likely have favorable toxicity profiles. “Caffeine is a nonselective antagonist of adenosine receptors that is very widely used with only minimal side effects,” such as insomnia, he said.

In August 2010, Linden and a researcher at the **University of Virginia School of Medicine** published in *Blood* that ADORA<sub>2A</sub> agonists reduced infiltration of proinflammatory NK and induced NK T (iNKT) cells into the lungs of mouse models of acute chest syndrome, thereby improving lung function and decreasing lung damage.<sup>2</sup> ADORA<sub>2A</sub> agonists thus could help treat vaso-occlusive crisis by reducing inflammatory responses, the team wrote in its report.

Based on those data plus the new findings in *Nature Medicine*, Linden thinks a good approach to sickle cell disease could be

**“An ADORA<sub>2B</sub> antagonist could prevent sickling and the inflammation that results from it, but once inflammation is full-blown during vaso-occlusive crisis, preventing sickling won’t be effective.”**

—John Magnani,  
GlycoMimetics Inc.

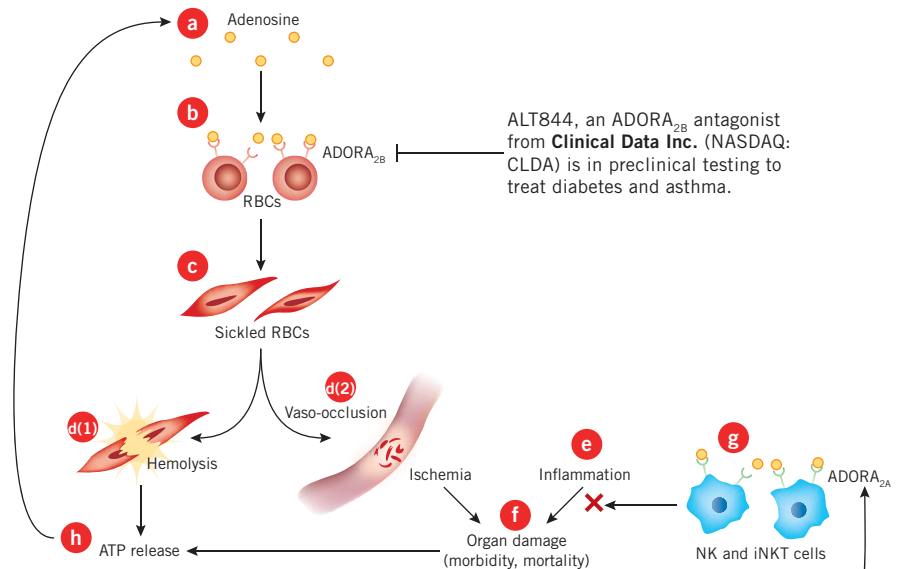
**Figure 1. Adenosine's sickle cell cycle.**

Targeting signaling between adenosine and its receptors could help decrease disease severity and mortality in sickle cell disease.

According to a *Nature Medicine* study, signaling between adenosine [a] in blood plasma and the adenosine A<sub>2B</sub> receptor (ADORA<sub>2B</sub>) on red blood cells (RBCs) [b] induces sickling of RBCs [c], which leads to hemolysis [d(1)] and/or vaso-occlusion [d(2)]. This results in ischemia/reperfusion, inflammation [e] and consequent damage to lungs and other organs [f].

According to a *Blood* study, in the lungs inflammation [e] that contributes to organ damage [f] can be decreased by agonizing ADORA<sub>2A</sub> on NK cells and induced NK T (iNKT) cells [g].

Additionally, both hemolysis [d(1)] and organ damage [f] result in the release of ATP [h] into the bloodstream, which metabolizes to adenosine [a] and thereby exacerbates the disease.



ALT844, an ADORA<sub>2B</sub> antagonist from **Clinical Data Inc.** (NASDAQ: CLDA) is in preclinical testing to treat diabetes and asthma.

Lexiscan regadenoson, an ADORA<sub>2A</sub> agonist from **Astellas Pharma Inc.** (Tokyo:4503) and **Gilead Sciences Inc.** (NASDAQ:GILD), is marketed for use as a myocardial perfusion imaging (MPI) agent, and is in Phase I testing to treat sickle cell disease. Stedivaze apadenoson, an ADORA<sub>2A</sub> agonist from Clinical Data, is in Phase III testing for use as an MPI agent. At least three other ADORA<sub>2A</sub> agonists are in preclinical testing: ALT1222 from Clinical Data to treat inflammatory disorders; ALT313 from Clinical Data to treat pain and B cell cancers; ALT313 from Clinical Data and **Santen Pharmaceutical Co. Ltd.** (Tokyo:4536; Osaka:4536) to treat glaucoma; and DT1133 from **Domain Therapeutics S.A.** to treat Parkinson's disease (PD).

“an ADORA<sub>2B</sub> antagonist for long-term disease management—as a prophylactic against red blood cell sickling—and administration of an ADORA<sub>2A</sub> agonist to treat” vaso-occlusive crises when they occur (see **Figure 1**, “Adenosine's sickle cell cycle”).

Linden was a cofounder of Adenosine Therapeutics LLC, a company that developed selective adenosine receptor–targeting therapies to treat cardiovascular, inflammatory, neurological and other diseases. The company was acquired by **Clinical Data Inc.** in 2008. The deal included Stedivaze apadenoson, an ADORA<sub>2A</sub> agonist that now is in Phase III testing as a pharmaceutical stress agent for cardiovascular imaging.

Adenosine Therapeutics also provided several preclinical candidates, of which the lead ADORA<sub>2B</sub> antagonist is ALT844 to treat asthma and diabetes.

LIAI is collaborating with the **Dana-Farber Cancer Institute** and other institutions in a Phase I trial of Lexiscan regadenoson, an ADORA<sub>2A</sub> agonist from **Gilead Sciences Inc.** and **Astellas Pharma Inc.**, to treat vaso-occlusion in sickle cell disease. According to Astellas spokesperson Jenny Keeney, the pharma provided some of the trial's funding but is otherwise not involved.

Gilead and Astellas market Lexiscan as a pharmaceutical stress agent for cardiovascular imaging.

The University of Texas Health Science Center has filed a patent

application for the findings reported in *Nature Medicine*, and Xia said the IP is available for licensing or partnering.

Haas, M.J. *SciBX* 4(3); doi:10.1038/scibx.2011.62  
Published online Jan. 20, 2011

**REFERENCES**

- Zhang, Y. *et al. Nat. Med.*; published online Dec. 19, 2010; doi:10.1038/nm.2280  
**Contact:** Yang Xia, The University of Texas Health Science Center at Houston, Houston, Texas  
e-mail: [yang.xia@uth.tmc.edu](mailto:yang.xia@uth.tmc.edu)
- Wallace, K.L. & Linden, J. *Blood* **166**, 5010–5020 (2010)

**COMPANIES AND INSTITUTIONS MENTIONED**

**Astellas Pharma Inc.** (Tokyo:4503), Tokyo, Japan  
**Central South University**, Changsha, China  
**Clinical Data Inc.** (NASDAQ:CLDA), Newton, Mass.  
**Dana-Farber Cancer Institute**, Boston, Mass.  
**The First Xiangya Hospital**, Changsha, China  
**Gilead Sciences Inc.** (NASDAQ:GILD), Foster City, Calif.  
**GlycoMimetics Inc.**, Gaithersburg, Md.  
**La Jolla Institute for Allergy & Immunology**, La Jolla, Calif.  
**Metabolon Inc.**, Research Triangle Park, N.C.  
**The Third Xiangya Hospital**, Changsha, China  
**University of Colorado Denver**, Denver, Colo.  
**The University of Texas Health Science Center at Houston**, Houston, Texas  
**University of Virginia School of Medicine**, Charlottesville, Va.

# Circulating translation

By Lauren Martz, Staff Writer

**Johnson & Johnson** has teamed up with **Massachusetts General Hospital** to develop and commercialize new technologies for capturing and characterizing circulating tumor cells. The partnership is the first under the hospital's translational research centers technology innovation initiative, which promotes industry alliances for early stage research projects. For the pharma, the deal is part of an external innovation strategy that is intended to lower the cost and improve the success rate of clinical development.

Circulating tumor cells (CTCs) break off from solid tumors and circulate in the bloodstream at very low levels. These cells have the potential to be used for noninvasive diagnosis of cancer and provide biological and genetic information about the tumors.

J&J is no stranger to the field, as its Veridex LLC diagnostic unit developed the first FDA-approved CTC product. The company launched its CellSearch System to identify and count CTCs in blood samples in 2004. The *in vitro* diagnostic is approved to predict prognosis for patients with metastatic breast, colorectal and prostate cancers.

According to Nic Dracopoli, VP of oncology biomarkers at J&J's Ortho Biotech unit, the company's existing CTC technology only counts circulating tumor cells in the blood. "The idea for the new technology is to make inferences about the tumor based on the molecular characterization of the CTCs and a better understanding of the molecular pathology underlying each patient's response to therapy and disease progression," he said. "Our current technology is observational. It doesn't let you isolate and characterize the cells easily or comprehensively."

"It is very well recognized that the existing CTC platforms have low efficiency of capture and only have the ability to process small blood volumes. The sensitivity and specificity of the existing systems need much improvement," said Frances Toneguzzo, executive director of Partners HealthCare Research Ventures & Licensing, which is the technology transfer arm for MGH and Brigham and Women's Hospital at **Harvard Medical School**.

MGH and J&J plan to develop a next-generation CTC platform capable of capturing, counting and characterizing tumor cells from whole blood with better specificity and selectivity.

"The goal is to bring to market over the next three to five years a next-generation platform that will change the current abilities of CTC technology," Dracopoli told *SciBX*.

The platform is a microchip involving magnetic bead technology for high-volume sorting and efficiency. MGH has filed patent applications covering the technology. Uma Sundaram, senior business strategy and licensing manager at MGH, said the IP is distinct from earlier CTC microchips developed at the hospital.

"What we are looking for is not just an incremental improvement," said Toneguzzo. "We are interested in orders-of-magnitude improvements over currently available CTC technologies. We aim to be able to process large quantities of blood, to collect the CTCs more efficiently and to collect functional and viable cells for biologic and genetic analysis."

## Starting early

The five-year collaboration will join researchers with CTC technology expertise from the MGH BioMicroElectroMechanical Systems (BioMEMS) Resource Center, clinical researchers and molecular biologists from the hospital's Cancer Center and R&D staff from two J&J units—Veridex and the Ortho Biotech Oncology R&D unit.

The partners plan to bring a CTC platform through the remaining preclinical work at MGH before handing the technology off to Veridex for clinical validation and regulatory submissions within three to five years. Veridex will market the resulting technology.

"The idea is to be working in a product development mode. Pairing product development engineers with academics, with a focus on a core technology, will help us guide the technology in the right direction from an early stage," said Toneguzzo.

"Academics aren't necessarily focused on milestones and deadlines, but bringing in people to work hand-in-hand with the researchers could help ease the transition," she continued. "We're targeting optimistically three years as the hand-off, and if that comes earlier, then we will be able to take the opportunity to continue to work closely with J&J through the clinical development phases."

"We hope that working together while the work is still in the preclinical stages will be more cost and time effective than traditional technology transfer," because companies that in-license products often have to repeat many of the studies run by the academic institutions, added Toneguzzo. "The goal of this type of partnership is for MGH to develop the technology further than we would normally go and to have the company step in earlier than they normally would."

"Johnson & Johnson evaluated a lot of potential opportunities," Dracopoli noted. "MGH has a third-generation technology that is very compatible with our existing platform from Veridex. They also have strong capability in terms of clinical testing and validation of the technology. What we really hope to achieve with this collaboration is a more thorough understanding of why drugs work in patients and why they don't. Academics put a lot of research into understanding patient responses to treatment, and we need to understand why resistance to therapy and disease progression occurs in each patient."

Dracopoli told *SciBX*, "I think our company's goal is to be doing increasingly more collaboration with academia."

Last June, J&J's Ortho-McNeil-Janssen Pharmaceuticals Inc. subsidiary entered a five-year joint cancer research agreement with the **Massachusetts Institute of Technology's** David H. Koch Institute for Integrative Cancer Research. The deal focuses on cancer diagnostics, the biology of premalignancies, genetic disease models and tumor microenvironment profiles.

Going forward, Toneguzzo said the hospital hopes to form similar deals with other companies. She said therapeutic areas for such deals include orthopedics, dermatology and additional applications within BioMEMS outside of cancer.

Financial terms of the J&J deal were not disclosed.

Martz, L. *SciBX* 4(3); doi:10.1038/scibx.2011.63  
Published online Jan. 20, 2010

## COMPANIES AND INSTITUTIONS MENTIONED

**Harvard Medical School**, Boston, Mass.

**Johnson & Johnson** (NYSE:JNJ), New Brunswick, N.J.

**Massachusetts General Hospital**, Boston, Mass.

**Massachusetts Institute of Technology**, Cambridge, Mass.

# Bacterial blood brain bypass

By Chris Cain, Staff Writer

A team at **Institut National de la Santé et de la Recherche Médicale** has identified a new mechanism that explains how meningococcus crosses the blood brain barrier. The researchers think the findings could be used to treat one form of meningococcal sepsis and may also have broader applications in delivering therapeutics into the CNS.

*Neisseria meningitidis* (meningococcus) is a bacterial pathogen that causes disease in about 1 in 100,000 people in the U.S. each year, primarily in children less than 1 year old. Although the disease is both rare and readily prevented with vaccines, researchers at the Institut National de la Santé et de la Recherche Médicale (INSERM) have maintained interest in the bacteria's rare ability to bypass the blood brain barrier (BBB) and induce swelling of the brain.

In 2009, an INSERM group published in *Science* that meningococcus bypasses the BBB by creating gaps in the normally impenetrable tight junctions that form the barrier's cell-cell interface.<sup>1</sup>

Now, the team has fleshed out the precise mechanism<sup>2</sup> (see **Figure 1**, “Breaching the blood brain barrier”). First, type IV pili, which are thread-like protein structures expressed on the bacterial surface, bind to adrenergic receptor  $\beta_2$  (ADRB2) expressed on the surface of cells lining the BBB. An ADRB2-associated scaffolding protein, arrestin  $\beta_2$  (ARRB2), then signals downstream to trigger rearrangement of the host cell cytoskeleton, stopping meningococcus from being washed away by the shear stress of blood flow against the barrier (see **Figure 1[a]**).

Next, ARRB2 recruits the tight junction proteins catenin (cadherin-associated protein)  $\delta 1$  (CTNND1; p120) and VE-cadherin (CD144; cadherin-5) away from the cell-cell interface to the site of bacterial adhesion (see **Figure 1[b]**). This weakens the tight junction and creates gaps in the BBB, which meningococcus can then invade (see **Figure 1[c]**).

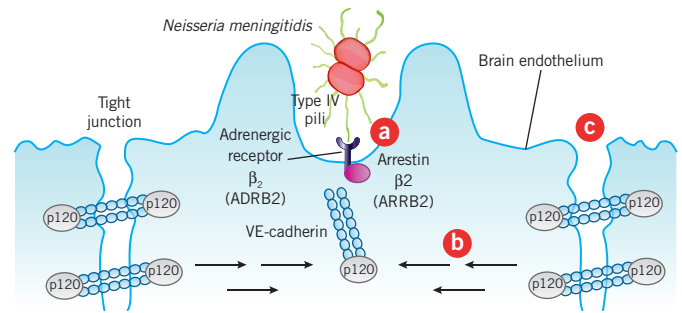
The researchers also showed that the generic adrenergic receptor  $\beta$  agonist isoproterenol prevented meningococcal invasion in a cell culture model of the BBB.

The findings were published in *Cell*.

Stefano Marullo, a research director at INSERM and senior author of the *Cell* paper, said the work may have therapeutic implications for some meningococcal-infected patients who experience sepsis.

“In a subset of patients you see the formation of red spots on the skin, known as purpura fulminans, which indicates that bacteria are causing the leakage of blood from the capillaries. This can kill a completely healthy person within four hours. Treatment with an adrenergic receptor  $\beta$  agonist would cause internalization of the receptor away from the cell surface and could rapidly treat these patients,” said Marullo.

He did say more work needs to be done to see if the drug affects peripheral capillaries in the same way it affects the distinct, tightly-knit capillaries that



**Figure 1. Breaching the blood brain barrier.**

line the BBB. At least 15 companies have adrenergic receptor  $\beta$  agonists in development or marketed to treat asthma and chronic obstructive pulmonary disease (COPD).

Xavier Nassif, a research director at INSERM, was a senior author on both publications and filed a patent covering the use of meningococcal pilin proteins to deliver therapeutics across the BBB.

“I could envision using a short, pilin-derived peptide of 20–30 amino acids to enable delivery of drugs, perhaps carried in liposomes, across the blood brain barrier,” he told *SciBX*.

Nassif said additional experiments need to be done, including testing purified pilin protein in cell culture and eventually in mouse models.

“One important experiment would be to show the offset of the effect: How long is the barrier open after giving pilin proteins? Ideally, to deliver a drug into the brain one would like to open the barrier long enough so that a drug can get in, but this should also be as short as possible to minimize the time during which plasma proteins or other compounds could get in the brain and cause damage,” said Bjoern Bauer, assistant professor in the College of Pharmacy at the **University of Minnesota**.

He also was concerned that purified protein may not specifically target the BBB, as many cells express *ADRB2*. This could cause side effects and would make specific delivery to the brain difficult, according to Bauer.

Bauer leads a research team focused on delivering drugs across the BBB. The group's strategy is to transiently inhibit drug efflux transporters, which would allow a window of time to deliver drugs into the CNS.

Nassif and Marullo now plan to map the pili-interacting region of *ADRB2* and in the future intend to further explore the signaling pathway triggered by pili binding to the receptor.

Cain, C. *SciBX* 4(3); doi:10.1038/scibx.2011.64

Published online Jan. 20, 2011

## REFERENCES

1. Coureuil, M. *et al. Science* **325**, 83–87 (2009)
  2. Coureuil, M. *et al. Cell*; published online Dec. 23, 2010; doi:10.1016/j.cell.2010.11.035
- Contact:** Stefano Marullo, University Paris Descartes and Cochin Institute, Paris, France  
e-mail: [stefano.marullo@inserm.fr](mailto:stefano.marullo@inserm.fr)

## COMPANIES AND INSTITUTIONS MENTIONED

**Institut National de la Santé et de la Recherche Médicale**, Paris, France  
**University of Minnesota**, Duluth, Minn.

# New and improved dystrophic mice

By **Tim Fulmer**, Senior Writer

California researchers have developed a new mouse model of Duchenne muscular dystrophy that better reflects the disease than current rodent models.<sup>1</sup> The team plans to use the model to identify combination therapies that not only correct the genetic defect underlying the disease but also block its progression.

The standard model of DMD is the *mdx* mouse, which carries the mutated *dystrophin* (*Dmd*; *mdx*) gene found in patients. However, there is a well-known discrepancy between the severe muscle weakness of DMD patients and the relatively mild symptoms of the *mdx* mouse.

A team led by Helen Blau and Jason Pomerantz hypothesized that differences in mouse and human telomeres might underlie the discrepancy. Telomeres are protein-DNA structures that cap the ends of chromosomes to protect them from damage and prevent instability of the genome. Excessive shortening of telomeres can lead to cellular senescence.<sup>2,3</sup>

Previous studies have shown that muscle cells from DMD patients have less potential to proliferate and regenerate,<sup>4,5</sup> which in some cases is associated with shortening of telomeres, than muscle cells from healthy subjects.<sup>6,7</sup>

The researchers decided to test their hypothesis by creating an *mdx* mouse with shortened telomeres. The resulting double knockout mice were deficient in *mdx* and *telomerase RNA component* (*Terc*; *mTR*), a portion of the telomerase enzyme that ensures chromosomes maintain proper telomere lengths.

Compared with single knockout and wild-type mice, the double knockouts showed increased disease severity based on several different criteria.

For example, the *mdx/mTR* mice had significantly higher levels of serum creatine kinase than control mice that lacked only *mdx* or only *mTR* ( $p < 0.05$  and  $p < 0.0001$ , respectively). Increased creatine kinase is a marker

of skeletal muscle damage in mice and is used to diagnose DMD.

The *mdx/mTR* mice also became exhausted more quickly on a treadmill than controls ( $p < 0.0001$  for both single knockout controls) and had more damage to their diaphragm and calf muscles, which showed extensive fibrosis, calcium deposits and immune cell infiltration. Finally, disease in the *mdx/mTR* mice progressed more rapidly with age and ultimately led to a shortened lifespan.

Further cell culture and *in vivo* studies showed that the severe disease phenotype in the double knockouts was associated with a decreased capacity of muscle stem cells to proliferate.

The authors wrote that the data "... indicate that the combination of the structural defect of dystrophin deficiency that leads to muscle degeneration together with the progressive exhaustion of functional MuSC [muscle stem cells] generates the dystrophic phenotype."

The findings were published in *Cell*.

"The findings from the *mdx/mTR* mice change the way we view treating Duchenne muscular dystrophy. We can no longer focus solely on correcting the dystrophin deficiency," Blau told *SciBX*. "Presumably the ideal therapeutic strategy should address a twofold deficiency—the lack of a functional *dystrophin* gene and the lack of muscle stem cells capable of proliferating and replenishing muscle tissue."

Blau is director of the Baxter Laboratory for Stem Cell Biology and a professor of microbiology and immunology at the **Stanford University School of Medicine**. Pomerantz is an assistant

professor in the Division of Plastic and Reconstructive Surgery at the **University of California, San Francisco**.

In a commentary accompanying the paper, Jeffrey Chamberlain wrote, "The *mdx/mTR* double-mutant mice increase the power of therapeutic testing by providing greater resolution between normal and dystrophic muscle function."<sup>8</sup> Chamberlain is a professor of neurology, medicine and biochemistry at the **University of Washington School of Medicine**.

## One-two punch for DMD

Blau and colleagues now want to use the mice as disease models to identify therapeutic strategies that target both aspects of DMD—loss of muscle cell regenerative capacity and dystrophin deficiency.

**"One can already imagine the general outlines of such a dual therapy—gene therapy to correct the dystrophin deficiency and stem cell therapy to correct the loss of muscle stem cells."**

—Helen Blau,  
Stanford University  
School of Medicine

## SciBX: Science–Business eXchange

Kick-start your knowledge management—and leave your competitors behind...

Can you afford not to subscribe?

Visit [scibx.com](http://scibx.com) for details on how to subscribe to SciBX

“One can already imagine the general outlines of such a dual therapy—gene therapy to correct the *dystrophin* deficiency and stem cell therapy to correct the loss of muscle stem cells,” Blau said.

Blau and Chamberlain have set up a collaboration to use the *mdx/mTR* mice to identify such dual therapies. The partnership combines Blau and Pomerantz’s focus on muscle stem cells with Chamberlain’s focus on gene therapy to treat muscular dystrophy.

In addition, the researchers want to use the mice to identify markers associated with muscle stem cell loss in disease and aging. “Based on the *Cell* paper, we already have one such marker—shortened telomere length,” Pomerantz told *SciBX*. “However, we gather from prior studies on muscle stem cell aging that there are multiple markers of loss of stem cell proliferative capacity, including elevated oxidative damage and increased levels of the tumor suppressor p16.”

Ideally, a panel of such biomarkers would allow staging of DMD progression, said Pomerantz. “Using the markers to help us differentiate early stage from late stage disease will probably be important to help guide the choice of the right DMD therapy,” he said.

Chamberlain agreed. In very young children with early stage disease, when the muscle stem cells have not yet become exhausted, gene therapy to correct the *dystrophin* deficiency might be sufficient, he said. In older children, in which disease has progressed and significant muscle stem cell exhaustion has occurred, dual gene therapy and cell therapy will likely be necessary, he said.

Finally, Blau said, a third area of interest is using the *mdx/mTR*

**“Using the markers to help us differentiate early stage from late stage disease will probably be important to help guide the choice of the right DMD therapy.”**

—Jason Pomerantz,  
University of California,  
San Francisco

mouse model to screen small molecule and peptide libraries for compounds that trigger endogenous muscle stem cells to proliferate.

“Such compounds could be valuable not only for preventing muscle stem cell exhaustion associated with muscular dystrophy but could also be useful for reversing muscle stem cell loss associated with injury and aging,” she said.

Blau said the findings published in *Cell* are covered by patents but declined to disclose further details.

Fulmer, T. *SciBX* 4(3); doi:10.1038/scibx.2011.65  
Published online Jan. 20, 2011

#### REFERENCES

1. Sacco, A. *et al. Cell*; published online Dec. 9, 2010; doi:10.1016/j.cell.2010.11.039  
**Contact:** Helen M. Blau, Stanford University School of Medicine, Stanford, Calif.  
e-mail: [hblau2@stanford.edu](mailto:hblau2@stanford.edu)  
**Contact:** Jason H. Pomerantz, University of California, San Francisco, Calif.  
e-mail: [jason.pomerantz@ucsfmedctr.org](mailto:jason.pomerantz@ucsfmedctr.org)
2. Sherr, C.J. & DePinho, R.A. *Cell* **102**, 407–410 (2000)
3. Rodier, F. *et al. Int. J. Biochem. Cell Biol.* **37**, 977–990 (2005)
4. Blau, H.M. *et al. Proc. Natl. Acad. Sci. USA* **80**, 4856–4860 (1983)
5. Webster, C. & Blau, H.M. *Somat. Cell Mol. Genet.* **16**, 557–565 (1990)
6. Decary, S. *et al. Neuromuscul. Disord.* **10**, 113–120 (2000)
7. Mouly, V. *et al. Acta Physiol. Scand.* **184**, 3–15 (2005)
8. Chamberlain, J.S. *Cell* **143**, 1040–1042 (2010)

#### COMPANIES AND INSTITUTIONS MENTIONED

Stanford University School of Medicine, Stanford, Calif.  
University of California, San Francisco, Calif.  
University of Washington School of Medicine, Seattle, Wash.

## Can You Afford Not to Read SciBX?

According to MEDLINE®, the U.S. National Library of Medicine’s® premier bibliographic database of articles in life sciences, over 775,000 articles were added to the database in 2009 alone—an average of almost 15,000 new articles every week.

Can you afford to miss investment opportunities?

Can you afford to miss emerging competition?

SciBX is the single source for scientific context, commercial impact and the critical next steps.

Visit [scibx.com](http://scibx.com) for details on how to subscribe to SciBX

**SciBX: Science–Business eXchange**

## This week in therapeutics

**THE DISTILLERY** brings you this week's most essential scientific findings in therapeutics, distilled by *SciBX* editors from a weekly review of more than 400 papers in 41 of the highest-impact journals in the fields of biotechnology, the life sciences and chemistry. The Distillery goes beyond the abstracts to explain the commercial relevance of featured research, including licensing status and companies working in the field, where applicable.

This week in therapeutics includes important research findings on targets and compounds, grouped first by disease class and then alphabetically by indication.

Indication	Target/marker/pathway	Summary	Licensing status	Publication and contact information
<b>Cancer</b>				
Brain cancer	Myeloid/lymphoid or mixed-lineage leukemia 2 (MLL2); MLL3	A genomic study suggests that agonizing the histone methyltransferases MLL2 or MLL3 could help treat medulloblastoma. In a genomic analysis of tumor tissue from children with medulloblastoma, 16% of patients had inactivating mutations in MLL2 or MLL3. Next steps include determining the specific function of those mutations in medulloblastomas.  <b>SciBX 4(3); doi:10.1038/scibx.2011.66</b> Published online Jan. 20, 2011	Patent pending; available for licensing from The Johns Hopkins University Technology Transfer Office	Parsons, D.W. <i>et al. Science</i> ; published online Dec.16, 2010; doi:10.1126/science.1198056 <b>Contact:</b> Victor E. Velculescu, The Johns Hopkins University School of Medicine, Baltimore, Md. e-mail: <a href="mailto:velculescu@jhmi.edu">velculescu@jhmi.edu</a> <b>Contact:</b> Kenneth W. Kinzler, same affiliation as above e-mail: <a href="mailto:kinzlike@jhmi.edu">kinzlike@jhmi.edu</a> <b>Contact:</b> Bert Vogelstein, same affiliation as above e-mail: <a href="mailto:vogelbe@gmail.com">vogelbe@gmail.com</a>
Cancer	CXC chemokine receptor 4 (CXCR4; NPY3R); VEGF; VEGF receptor 1 (FLT1; VEGFR-1)	Studies in mice suggest that combined inhibition of CXCR4 and VEGFR-1 could help treat cancer. In mice bearing prostate or breast cancer cell lines and lacking the kinase domain of Vegfr-1, the CXCR4 inhibitor AMD3100 decreased tumor volume and metastasis compared with those in mice with wild-type Vegfr-1. Next steps include testing the use of CXCR4 blockade to prevent resistance to anti-VEGF therapy in glioblastoma, colorectal and liver cancer models. Mozobil plerixafor (AMD3100), a CXCR4 antagonist from Genzyme Corp., is approved in the U.S. to mobilize stem cells for transplant in non-Hodgkin's lymphoma (NHL) and multiple myeloma (MM) patients. At least seven companies have CXCR4 antagonists in preclinical to Phase I development for cancer.  <b>SciBX 4(3); doi:10.1038/scibx.2011.67</b> Published online Jan. 20, 2011	Patent application filed for the combinatorial use of anti-CXCR4 therapy with other anticancer therapies; available for licensing <b>Contact:</b> Lambert Edelmann, Partners HealthCare, Boston, Mass. e-mail: <a href="mailto:ledelman@partners.org">ledelman@partners.org</a>	Hiratsuka, S. <i>et al. Proc. Natl. Acad. Sci. USA</i> ; published online Dec. 20, 2010; doi:10.1073/pnas.1016917108 <b>Contact:</b> Rakesh K. Jain, Harvard Medical School, Boston, Mass. e-mail: <a href="mailto:jain@steele.mgh.harvard.edu">jain@steele.mgh.harvard.edu</a>
<b>Cardiovascular disease</b>				
Atherosclerosis	Apolipoprotein E (APOE); cyclophilin A (PPIA; CYPA)	Studies in mice suggest that inhibiting PPIA could help treat atherosclerosis. In <i>ApoE</i> -deficient mice fed a high-cholesterol diet, genetic loss of <i>Ppia</i> resulted in smaller atherosclerotic lesions than those in controls with functional <i>Ppia</i> . Next steps could include identifying selective and specific <i>PPIA</i> inhibitors and evaluating their effects in the mouse model.  <b>SciBX 4(3); doi:10.1038/scibx.2011.68</b> Published online Jan. 20, 2011	Patent and licensing status unavailable	Nigro, P. <i>et al. J. Exp. Med.</i> ; published online Dec. 12, 2010; doi:10.1084/jem.20101174 <b>Contact:</b> Bradford C. Berk, The School of Medicine and Dentistry at the University of Rochester, Rochester, N.Y. e-mail: <a href="mailto:bradford_berk@urmc.rochester.edu">bradford_berk@urmc.rochester.edu</a>

## This week in therapeutics (continued)

Indication	Target/marker/ pathway	Summary	Licensing status	Publication and contact information
Ischemia; reperfusion injury	Macrophage migration inhibitory factor (MIF)	Studies in rats suggest that MIF-binding benzothiazin-4-one derivatives could help prevent ischemia and reperfusion injury. In a rat model of ischemia and reperfusion injury, one of the derivatives led to about 45% smaller infarct sizes than vehicle controls ( $p=0.0013$ ). In cultured cardiomyocytes, a second benzothiazin-4-one derivative bound MIF and activated gene expression to prevent apoptosis compared with no treatment. Next steps include testing whether the derivatives can prevent compensatory cardiac hypertrophy from progressing to heart failure. Takeda Pharmaceutical Co. Ltd. did not disclose the developmental status of its benzothiazin-4-one derivatives program.  <b>SciBX 4(3); doi:10.1038/scibx.2011.69</b> <b>Published online Jan. 20, 2011</b>	Patent application filed; unavailable for licensing	Kimura, H. <i>et al. Chem. Biol.</i> ; published online Dec. 22, 2010; doi:10.1016/j.chembiol.2010.10.011 <b>Contact:</b> Haruhide Kimura, Takeda Pharmaceutical Co. Ltd., Osaka, Japan e-mail: <a href="mailto:kimura_haruhide@takeda.co.jp">kimura_haruhide@takeda.co.jp</a>
Myocardial infarction (MI)	MicroRNA-499 (miR-499)	<i>In vitro</i> and mouse studies suggest that increasing miR-499 activity in the heart could improve recovery from MI. In cardiomyocytes, expression of wild-type miR-499 prevented apoptosis compared with expression of mutant miR-499. In a mouse model of ischemic injury, an miR-499 antagomir increased infarct size and abnormal cardiac remodeling, whereas miR-499 overexpression decreased injury. Next steps could include further testing to understand how the pathway causes miR-499-mediated protection from apoptosis.  <b>SciBX 4(3); doi:10.1038/scibx.2011.70</b> <b>Published online Jan. 20, 2011</b>	Patent and licensing status unavailable	Wang, J.-X. <i>et al. Nat. Med.</i> ; published online Dec. 26, 2010; doi:10.1038/nm.2282 <b>Contact:</b> Pei-Feng Li, Institute of Zoology, Chinese Academy of Sciences, Beijing, China e-mail: <a href="mailto:peifli@ioz.ac.cn">peifli@ioz.ac.cn</a>
Myocardial infarction (MI)	Protein kinase C (PKC)	<i>In vitro</i> and rat studies suggest that implanted mesenchymal stem cells that have been treated with a PKC activator could help treat MI. In isolated mesenchymal stem cells, the PKC activator phorbol myristate acetate induced expression of cardiogenic markers. In rats with infarcted hearts, implantation of the treated cells improved cardiac remodeling and decreased infarct size compared with implantation of untreated mesenchymal stem cells. The treated cells also reduced arrhythmias and prevented sudden death compared with untreated cells. Next steps could include additional studies on phorbol myristate acetate-induced conversion of mesenchymal stem cells.  <b>SciBX 4(3); doi:10.1038/scibx.2011.71</b> <b>Published online Jan. 20, 2011</b>	Patent and licensing status unavailable	Song, H. <i>et al. Proc. Natl. Acad. Sci. USA</i> ; published online Dec. 20, 2010; doi:10.1073/pnas.1015873107 <b>Contact:</b> Yangsoo Jang, Yonsei University College of Medicine, Seoul, South Korea e-mail: <a href="mailto:jangys1212@yuhs.ac">jangys1212@yuhs.ac</a> <b>Contact:</b> Sung-Hou Kim, University of California, Berkeley, Calif. e-mail: <a href="mailto:shkim@cchem.berkeley.edu">shkim@cchem.berkeley.edu</a>

## This week in therapeutics (continued)

Indication	Target/marker/ pathway	Summary	Licensing status	Publication and contact information
<b>Gastrointestinal disease</b>				
Colitis	Tryptase $\beta$ 2 (TPSB2)	<p>Studies in mice suggest that inhibiting TPSB2 could help prevent colitis. In two mouse models of acute experimental colitis, <i>Tpsb2</i> deficiency resulted in fewer disease symptoms than no deficiency (<math>p &lt; 0.0001</math>). Next steps include developing and evaluating mast cell tryptase inhibitors in experimental colitis models.</p> <p><b>SciBX 4(3); doi:10.1038/scibx.2011.72</b> Published online Jan. 20, 2011</p>	Unpatented; licensing status undisclosed	<p>Hamilton, M.J. <i>et al.</i> <i>Proc. Natl. Acad. Sci. USA</i>; published online Dec. 20, 2010; doi:10.1073/pnas.1005758108 <b>Contact:</b> Matthew J. Hamilton, Harvard Medical School, Boston, Mass. e-mail: <a href="mailto:mjhamilton@partners.org">mjhamilton@partners.org</a></p>
<b>Infectious disease</b>				
Anthrax	Not applicable	<p><i>In vitro</i> and rat studies suggest that a combination of Ridaura auranofin and Catena idebenone could help prevent anthrax infection. In mouse macrophages, the small molecules auranofin and idebenone blocked cytotoxicity induced by the <i>Bacillus anthracis</i> lethal toxin (LT) compared with either drug alone. In rats, pretreatment with auranofin increased survival following LT exposure compared with no treatment. Next steps could include testing the combination in animal models of anthrax infection.</p> <p>Santhera Pharmaceuticals Holding AG and Takeda Pharmaceutical Co. Ltd. market Catena idebenone to treat ataxia. Prometheus Laboratories Inc. markets Ridaura auranofin to treat rheumatoid arthritis (RA).</p> <p><b>SciBX 4(3); doi:10.1038/scibx.2011.73</b> Published online Jan. 20, 2011</p>	Patent and licensing status unavailable	<p>Newman, Z.L. <i>et al.</i> <i>Antimicrob. Agents Chemother.</i>; published online Dec. 13, 2010; doi:10.1128/AAC.00772-10 <b>Contact:</b> Lisa M. Johansen, Zalicus Inc., Cambridge, Mass. e-mail: <a href="mailto:ljohansen@zalicus.com">ljohansen@zalicus.com</a></p>
HIV/AIDS	HIV capsid protein	<p><i>In vitro</i> studies identified HIV capsid protein inhibitors that could help treat HIV. In antiviral assays of peripheral blood mononuclear cells (PBMCs), compounds that bound a pocket in the N-terminal domain of the HIV capsid protein inhibited entry of HIV-1 and HIV-2 strains and HIV-1 clinical isolates compared with no treatment. Next steps include testing the inhibitors in animal models of HIV infection.</p> <p>Myrex Inc. has the oral HIV capsid protein inhibitor bevirimat dimeglumine in Phase II testing for the indication.</p> <p>Panacos Pharmaceuticals Inc. has the tablet form of bevirimat in Phase II testing to treat HIV.</p> <p><b>SciBX 4(3); doi:10.1038/scibx.2011.74</b> Published online Jan. 20, 2011</p>	Patent and licensing status unavailable	<p>Blair, W.S. <i>et al.</i> <i>PLoS Pathog.</i>; published online Dec. 9, 2010; doi:10.1371/journal.ppat.1001220 <b>Contact:</b> Scott L. Butler, Pfizer Global Research and Development, Sandwich, U.K. e-mail: <a href="mailto:scott.butler@pfizer.com">scott.butler@pfizer.com</a></p>
Meningitis	Adrenergic receptor $\beta_2$ (ADRB2)	<p>Cell culture studies suggest that agonizing ADRB2 could help treat or prevent meningitis caused by <i>Neisseria meningitidis</i> infection. In a cell culture model of the blood brain barrier, the generic ADRB2 agonist isoproterenol decreased both the number of <i>N. meningitidis</i>-induced gaps between cells and bacterial migration through the barrier compared with no treatment. Next steps include identifying the specific region of ADRB2 bound by <i>N. meningitidis</i>.</p> <p>At least 15 companies have ADRB2 agonists from preclinical to marketed to treat asthma or chronic obstructive pulmonary disease (COPD; see <b>Bacterial blood brain bypass</b>, page 5).</p> <p><b>SciBX 4(3); doi:10.1038/scibx.2011.75</b> Published online Jan. 20, 2011</p>	Patent application filed; available for licensing	<p>Coureuil, M. <i>et al.</i> <i>Cell</i>; published online Dec. 23, 2010; doi:10.1016/j.cell.2010.11.035 <b>Contact:</b> Stefano Marullo, University Paris Descartes and Cochin Institute, Paris, France e-mail: <a href="mailto:stefano.marullo@inserm.fr">stefano.marullo@inserm.fr</a></p>

## This week in therapeutics (continued)

Indication	Target/marker/ pathway	Summary	Licensing status	Publication and contact information
<b>Inflammation</b>				
Inflammation	Purinergic receptor P2Y G protein-coupled 6 (P2RY6; P2Y6)	Studies in mice suggest that inhibiting <i>P2Y6</i> could help treat vascular inflammation. In a mouse model of lipopolysaccharide (LPS)-induced vascular inflammation, a <i>P2Y6</i> antagonist lowered levels of a proinflammatory neutrophil cytokine in serum compared with vehicle control. In <i>P2y6</i> -deficient mice injected with LPS, serum levels of proinflammatory factors were lower than those in wild-type controls. Next steps include studying the role of <i>P2Y6</i> signaling in ventilator-induced lung injury.  <b>SciBX 4(3); doi:10.1038/scibx.2011.76</b> <b>Published online Jan. 20, 2011</b>	Work unpatented; licensing status not applicable	Riegel, A.-K. <i>et al. Blood</i> ; published online Dec. 20, 2010; doi:10.1182/blood-2010-10-313957 <b>Contact:</b> Holger K. Eltzschig, University of Colorado Denver, Aurora, Colo. e-mail: <a href="mailto:holger.eltzschig@ucdenver.edu">holger.eltzschig@ucdenver.edu</a>
<b>Metabolic disease</b>				
Hypercholesterolemia	Low-density lipoprotein receptor (LDLR)	<i>In vitro</i> studies suggest that duplex RNA could activate LDLR expression to help treat hypercholesterolemia. In cultured human liver cells, small RNA duplexes complementary to the LDLR promoter produced increases in cell surface expression of LDLR that were comparable to those produced by the generic cholesterol drug lovastatin. In the same cells, a combination of RNA duplexes and lovastatin increased LDLR expression compared with either agent alone. Next steps include testing duplex RNA-based gene activation with other targets.  <b>SciBX 4(3); doi:10.1038/scibx.2011.77</b> <b>Published online Jan. 20, 2011</b>	Patent application filed; licensed to Alnylam Pharmaceuticals Inc.	Matsui, M. <i>et al. Chem. Biol.</i> ; published online Dec. 22, 2010; doi:10.1016/j.chembiol.2010.10.009 <b>Contact:</b> David R. Corey, The University of Texas Southwestern Medical Center at Dallas, Dallas, Texas e-mail: <a href="mailto:david.corey@utsouthwestern.edu">david.corey@utsouthwestern.edu</a>
<b>Neurology</b>				
Alzheimer's disease (AD)	CREB binding protein (CREBBP; CBP)	A study in mice suggests that increasing CBP levels in the hippocampus could help treat AD. In a mouse model of AD, injection of CBP-expressing lentivirus into the hippocampus improved learning and memory deficits compared with injection of saline control. Next steps include determining whether the therapeutic effects of CBP are mediated by the CREB transcription factor or by a histone acetyltransferase.  <b>SciBX 4(3); doi:10.1038/scibx.2011.78</b> <b>Published online Jan. 20, 2011</b>	Unpatented; licensing status not applicable	Caccamo, A. <i>et al. Proc. Natl. Acad. Sci. USA</i> ; published online Dec. 13, 2010; doi:10.1073/pnas.1012851108 <b>Contact:</b> Salvatore Oddo, University of Texas Health Science Center at San Antonio, San Antonio, Texas e-mail: <a href="mailto:oddo@uthscsa.edu">oddo@uthscsa.edu</a>

## This week in therapeutics (continued)

Indication	Target/marker/pathway	Summary	Licensing status	Publication and contact information
Cognitive dysfunction	Glycine transporter type 1 (GLYT1)	A study in mice identified a triazole-based GLYT1-selective inhibitor that could help treat cognitive dysfunction. In a mouse model of the condition, the GLYT1 inhibitor decreased learning impairments compared with vehicle controls. Next steps could include evaluating the lead GLYT1 inhibitor in additional animal models of cognitive dysfunction. Astellas Pharma Inc. did not disclose next steps. R1678, a GLYT1 inhibitor from Roche, is in Phase II testing to treat schizophrenia. Org 25935, a GLYT1 inhibitor from Merck & Co. Inc., is in Phase II testing to treat panic disorder and Phase I trials for cognitive dysfunction. GSK1018921, a GLYT1 inhibitor from GlaxoSmithKline plc, is in Phase I testing to treat schizophrenia.  <b>SciBX 4(3); doi:10.1038/scibx.2011.79</b> <b>Published online Jan. 20, 2011</b>	Patented; licensing status unavailable	Sugane, T. <i>et al. J. Med. Chem.</i> ; published online Dec. 9, 2010; doi:10.1021/jm101031u <b>Contact:</b> Takashi Sugane, Astellas Pharma Inc., Ibaraki, Japan e-mail: <a href="mailto:takashi.sugane@jp.astellas.com">takashi.sugane@jp.astellas.com</a>
Pain	$\mu$ -Opioid receptor (OPRM1; MOR); opioid receptor- $\delta$ 1 (OPRD1; DOR)	Studies in mice identified tetrapeptide bifunctional agonists of OPRM1 and OPRD1 that could help treat neuropathic pain. <i>In vitro</i> , the lead compound inhibited both opioid receptors with subnanomolar EC <sub>50</sub> values. In mouse models of spinal cord injury, induced thermal hypersensitivity and tactile allodynia, the inhibitor decreased paw withdrawal responses compared with vehicle control. Next steps include further optimization of the compound's oral bioavailability.  <b>SciBX 4(3); doi:10.1038/scibx.2011.80</b> <b>Published online Jan. 20, 2011</b>	Unpatented; licensing status undisclosed	Lee, Y.S. <i>et al. J. Med. Chem.</i> ; published online Dec. 3, 2010; doi:10.1021/jm100982d <b>Contact:</b> Victor J. Hruby, The University of Arizona, Tucson, Ariz. e-mail: <a href="mailto:hruby@u.arizona.edu">hruby@u.arizona.edu</a>
<b>Ophthalmic disease</b>				
Age-related macular degeneration (AMD); ophthalmic disease	Mammalian target of rapamycin (mTOR; FRAP; RAFT1)	A study in mice suggests that mTOR inhibitors could help treat retinal degeneration. In a mouse model of oxidative stress-induced retinal degeneration, the mTOR inhibitor rapamycin increased retinal length, photoreceptor density and preserved photoreceptor function compared with vehicle control. Next steps could include testing additional mTOR inhibitors in mouse models of AMD. Pfizer Inc. markets Rapamune rapamycin (sirolimus) to prevent organ rejection in renal transplantation. The National Eye Institute is sponsoring a Phase I/II trial of sirolimus to treat AMD.  <b>SciBX 4(3); doi:10.1038/scibx.2011.81</b> <b>Published online Jan. 20, 2011</b>	Patent and licensing status unavailable	Zhao, C. <i>et al. J. Clin. Invest.</i> ; published online Dec. 6, 2010; doi:10.1172/JCI44303 <b>Contact:</b> Douglas Vollrath, Stanford University School of Medicine, Stanford, Calif. e-mail: <a href="mailto:vollrath@stanford.edu">vollrath@stanford.edu</a>

## This week in therapeutics (continued)

Indication	Target/marker/ pathway	Summary	Licensing status	Publication and contact information
<b>Pulmonary disease</b>				
Pulmonary fibrosis	Transforming growth factor- $\beta$ receptor II (TGFB $\beta$ 2; TGFB $\beta$ -RII)	<p>A study in mice suggests that antagonizing TGFB<math>\beta</math>2 could help treat idiopathic pulmonary fibrosis (IPF). In a mouse model of pulmonary fibrosis, TGFB<math>\beta</math>2 deficiency in the lung epithelium decreased lung damage and increased survival compared with no TGFB<math>\beta</math>2 deficiency. Next steps include developing antibodies that block TGFB<math>\beta</math>2.</p> <p><b>SciBX 4(3); doi:10.1038/scibx.2011.82</b> Published online Jan. 20, 2011</p>	Patent and licensing status undisclosed	<p>Li, M. <i>et al. J. Clin. Invest.</i>; published online Dec. 6, 2010; doi:10.1172/JCI42090</p> <p><b>Contact:</b> Parviz Minoo, University of Southern California, Los Angeles, Calif. e-mail: <a href="mailto:minoo@usc.edu">minoo@usc.edu</a></p> <p><b>Contact:</b> Zea Borok, Keck School of Medicine of the University of Southern California, Los Angeles, Calif. e-mail: <a href="mailto:zborok@usc.edu">zborok@usc.edu</a></p>
<b>Various</b>				
Leukemia; neurology	Janus kinase-3 (JAK-3)	<p>A study in cell culture and in mice suggests that JAK-3 inhibitors could help treat diseases caused by human T cell lymphotropic virus-1 (HTLV-1), including adult T cell leukemia and HTLV-1-associated myelopathy/tropical spastic paraparesis. In peripheral blood mononuclear cells (PBMCs) from patients with those two diseases, the JAK inhibitor tasocitinib (CP-690,550) decreased aberrant PBMC proliferation compared with no treatment. In a mouse model of T cell leukemia, tasocitinib increased survival compared with vehicle. Next steps include clinical trials of tasocitinib.</p> <p>Tasocitinib, an oral pan-JAK inhibitor from Pfizer Inc., is in Phase II/III testing for various autoimmune indications, dry eye and organ transplant rejection.</p> <p>VX-509, a JAK-3 inhibitor from Vertex Pharmaceuticals Inc., is in preclinical and Phase I/II testing for multiple autoimmune indications.</p> <p><b>SciBX 4(3); doi:10.1038/scibx.2011.83</b> Published online Jan. 20, 2011</p>	Patent status undisclosed; available for licensing	<p>Ju, W. <i>et al. Blood</i>; published online Nov. 24, 2010; doi:10.1182/blood-2010-09-305425</p> <p><b>Contact:</b> Thomas A. Waldmann, National Institutes of Health, Bethesda, Md. e-mail: <a href="mailto:tawald@helix.nih.gov">tawald@helix.nih.gov</a></p>

## This week in techniques

**THE DISTILLERY** brings you this week's most essential scientific findings in techniques, distilled by *SciBX* editors from a weekly review of more than 400 papers in 41 of the highest-impact journals in the fields of biotechnology, the life sciences and chemistry. The Distillery goes beyond the abstracts to explain the commercial relevance of featured research, including licensing status and companies working in the field, where applicable.

This week in techniques includes findings about research tools, disease models and manufacturing processes that have the potential to enable or improve all stages of drug discovery and development.

Approach	Summary	Licensing status	Publication and contact information
<b>Disease models</b>			
Mouse model of Duchenne muscular dystrophy (DMD)	An improved mouse model of DMD could aid the development of new treatments for the disease. The standard <i>mdx</i> mouse model of DMD lacks a functional dystrophin protein and generates mild DMD symptoms compared with those in patients. In the new mouse model, an additional deletion of the RNA component of telomerase led to greater disease severity than that in the <i>mdx</i> mouse. Also in the new model, muscle stem cell proliferation following tissue damage was lower than that in control <i>mdx</i> mice, suggesting that impaired muscle stem cell proliferation may drive disease progression. Next steps include using the new model to test DMD therapies ( <i>see New and improved dystrophic mice, page 6</i> ).	Patented; available for licensing	Sacco, A. <i>et al. Cell</i> ; published online Dec. 9, 2010; doi:10.1016/j.cell.2010.11.039 <b>Contact:</b> Helen M. Blau, Stanford University School of Medicine, Stanford, Calif. e-mail: <a href="mailto:hblau2@stanford.edu">hblau2@stanford.edu</a> <b>Contact:</b> Jason H. Pomerantz, University of California, San Francisco, Calif. e-mail: <a href="mailto:jason.pomerantz@ucsfmedctr.org">jason.pomerantz@ucsfmedctr.org</a>
Mouse model of medulloblastoma subtypes	Mouse models of medulloblastoma subtypes could guide the development of therapies specific for different forms of the disease. In patients, MRI studies showed that <i>wingless-type MMTV integration site (WNT)</i> pathway-driven medulloblastomas occurred in the fourth brain ventricle and infiltrated the dorsal brainstem, whereas <i>sonic hedgehog homolog (SHH)</i> pathway-driven medulloblastomas occurred in the cerebellar hemispheres and did not infiltrate the dorsal brainstem. In mice expressing a mutation in the <i>Wnt</i> pathway, medulloblastomas mimicked anatomical and genetic features of <i>WNT</i> pathway-driven medulloblastomas in humans. Next steps include using the mutant model to screen for compounds that are effective against <i>WNT</i> -driven medulloblastomas.	Work unpatented; available for licensing from the St. Jude Children's Research Hospital Office of Technology Licensing	Gibson, P. <i>et al. Nature</i> ; published online Dec. 8, 2010; doi:10.1038/nature09587 <b>Contact:</b> Richard J. Gilbertson, St. Jude Children's Research Hospital, Memphis, Tenn. e-mail: <a href="mailto:richard.gilbertson@stjude.org">richard.gilbertson@stjude.org</a>
<b>Drug delivery</b>			
Macroporous ferrogel scaffold for magnetic field-inducible drug or cell delivery	Macroporous ferrogels could be useful for externally controlled drug release. <i>In vitro</i> , macroporous ferrogels loaded with mitoxantrone, plasmid DNA or a chemokine showed greater release of the test compound in the presence of an external magnetic field than when no magnetic field was used. In mice given subcutaneously implanted mesenchymal stem cell-loaded ferrogels, magnetic stimulation induced a large release of cells from the scaffold compared with no magnetic stimulation, which led to almost no cell release. Next steps could include testing the efficacy of the scaffold for <i>in vivo</i> therapeutic drug delivery.	Patent and licensing status unavailable	Zhao, X. <i>et al. Proc. Natl. Acad. Sci. USA</i> ; published online Dec. 13, 2010; doi:10.1073/pnas.1007862108 <b>Contact:</b> David J. Mooney, Harvard University, Cambridge, Mass. e-mail: <a href="mailto:mooneyd@seas.harvard.edu">mooneyd@seas.harvard.edu</a>
Transferrin-mimicking peptide for delivery of brain cancer therapeutics or imaging agents	A transferrin-mimicking peptide could be useful for delivering therapeutic and imaging agents to brain tumors. In a mouse model of glioblastoma, a transferrin-mimicking peptide crossed the blood brain barrier and accumulated preferentially in tumors compared with in healthy brain tissue. Also in the mouse model, an adeno-associated viral (AAV) vector expressing the peptide and payload decreased tumor growth compared with the same vector not expressing the peptide. Ongoing studies include using the peptide for selective delivery of small interfering RNA, nanoparticles and other therapeutic and imaging agents to brain tumors.	Patented by The University of Texas M.D. Anderson Cancer Center; licensed to Mercator Therapeutics Inc.	Staquicini, F.I. <i>et al. J. Clin. Invest.</i> ; published online Dec. 22, 2010; doi:10.1172/JCI44798 <b>Contact:</b> Renata Pasqualini, The University of Texas M.D. Anderson Cancer Center, Houston, Texas e-mail: <a href="mailto:rpasqual@mdanderson.org">rpasqual@mdanderson.org</a> <b>Contact:</b> Wadih Arap, same affiliation as above e-mail: <a href="mailto:warap@mdanderson.org">warap@mdanderson.org</a>

## This week in techniques (continued)

Approach	Summary	Licensing status	Publication and contact information
<b>Drug platforms</b>			
Disruption of protein-protein interactions using pyrrolopyrimidine based $\alpha$ -helix peptide mimetics	<p>Pyrrolopyrimidine-based <math>\alpha</math>-helix peptide mimetics could provide a scaffold for developing small molecule inhibitors of protein-protein interactions. A screen of 900 pyrrolopyrimidine-derived compounds identified two leads that inhibited tumor protein p53 (TP53; p53) protein-protein interactions at submicromolar concentrations. In human lung cancer cells, the compounds increased p53 levels and proapoptotic caspase activity compared with an inactive control compound. Next steps include screening a larger library of pyrrolopyrimidine-based compounds to identify inhibitors of additional protein-protein interactions.</p> <p><b>SciBX 4(3); doi:10.1038/scibx.2011.88</b>  <b>Published online Jan. 20, 2011</b></p>	Patent application filed; licensing status undisclosed	<p>Lee, J.H. <i>et al. J. Am. Chem. Soc.</i>; published online Dec. 20, 2010; doi:10.1021/ja108230s  <b>Contact:</b> Hyun-Suk Lim, Indiana University School of Medicine, Indianapolis, Ind.  e-mail: <a href="mailto:limhyun@iupui.edu">limhyun@iupui.edu</a>  <b>Contact:</b> Hua Lu, same affiliation as above  e-mail: <a href="mailto:hualu@iupui.edu">hualu@iupui.edu</a></p>
Peptide activators of invariant NK T (iNKT) cells	<p>A study in cell culture and in mice suggests that peptide activators of iNKT cells could help treat autoimmune diseases, inflammatory diseases and transplant rejection. In mouse models of inflammation, collagen-induced arthritis and experimental autoimmune encephalomyelitis (EAE), vaccination with an iNKT cell-activating peptide improved disease compared with vaccination using a control peptide. Next steps include identifying peptides that can activate iNKT cells in humans.</p> <p>Acellera Therapeutics Ltd. has undisclosed agents that promote iNKT cell activation in preclinical development for liver transplantation and inflammation.</p> <p><b>SciBX 4(3); doi:10.1038/scibx.2011.89</b>  <b>Published online Jan. 20, 2011</b></p>	Unpatented; licensing status not applicable	<p>Liu, Y. <i>et al. J. Clin. Invest.</i>; published online Dec. 13, 2010; doi:10.1172/JCI43964  <b>Contact:</b> Shohreh Issazadeh-Navikas, University of Copenhagen, Copenhagen, Denmark  e-mail: <a href="mailto:shohreh.issazadeh@bric.ku.dk">shohreh.issazadeh@bric.ku.dk</a></p>
<b>Markers</b>			
A truncated form of chemokine CXC motif ligand 10 (CXCL10; IP-10) as a marker for nonresponsiveness to HCV therapy	<p>Studies in patients suggest that plasma levels of a truncated form of CXCL10 could help identify nonresponders to HCV therapy. In HCV patients receiving standard therapy of interferon plus ribavirin, nonresponders had higher plasma levels of a truncated form of CXCL10 and greater total CXCL10 levels than responders (<math>p=0.04</math> and <math>p=0.01</math>, respectively). Next steps include a validation study using additional patient samples.</p> <p>Rules-Based Medicine Inc., which uses its Multi-Analyte Profiling (MAP) technology platform to detect and analyze biomarkers, has rights to the findings.</p> <p><b>SciBX 4(3); doi:10.1038/scibx.2011.90</b>  <b>Published online Jan. 20, 2011</b></p>	Multiple patents covering use of $\text{NH}_2$ -truncated CXCL10 as a predictor for HCV as well as other chronic inflammatory diseases; licensed to Rules-Based Medicine	<p>Casrouge, A. <i>et al. J. Clin. Invest.</i>; published online Dec. 22, 2010; doi:10.1172/JCI40594  <b>Contact:</b> Matthew L. Albert, Pasteur Institute, Paris, France  e-mail: <a href="mailto:albertm@pasteur.fr">albertm@pasteur.fr</a></p>

**Company and institution index**

<b>A</b>	
Acellera Therapeutics Ltd.	15
Alnylam Pharmaceuticals Inc.	11
Astellas Pharma Inc.	3,12
<b>C</b>	
Central South University	2
Clinical Data Inc.	3
<b>D</b>	
Dana-Farber Cancer Institute	3
Domain Therapeutics S.A.	3
<b>F</b>	
First Xiangya Hospital	2
<b>G</b>	
Genzyme Corp.	8
Gilead Sciences Inc.	3
GlaxoSmithKline plc	12
GlycoMimetics Inc.	2
<b>H</b>	
Harvard Medical School	4
<b>I</b>	
Institut National de la Santé et de la Recherche Médicale	5
<b>J</b>	
Johns Hopkins University	8
Johnson & Johnson	4
<b>L</b>	
La Jolla Institute for Allergy & Immunology	2
<b>M</b>	
Massachusetts General Hospital	4
Massachusetts Institute of Technology	4
Mercator Therapeutics Inc.	14
Merck & Co. Inc.	12
Metabolon Inc.	2
Myrex Inc.	10
<b>N</b>	
National Eye Institute	12
<b>P</b>	
Panacos Pharmaceuticals Inc.	10
Pfizer Inc.	12,13
Prometheus Laboratories Inc.	10
<b>R</b>	
Roche	12
Rules-Based Medicine Inc.	15
<b>S</b>	
Santen Pharmaceutical Co. Ltd.	3
Santhera Pharmaceuticals Holding AG	10
Stanford University School of Medicine	6
St. Jude Children's Research Hospital	14
<b>T</b>	
Takeda Pharmaceutical Co. Ltd.	9,10

Third Xiangya Hospital	2
<b>U</b>	
University of California, San Francisco	6
University of Colorado Denver	2
University of Minnesota	5
University of Texas M.D. Anderson Cancer Center	14
University of Texas Health Science Center at Houston	2
University of Virginia School of Medicine	2
University of Washington School of Medicine	6

<b>V</b>	
Vertex Pharmaceuticals Inc.	13

.....

**Target and compound index**

<b>A</b>	
Adenosine	1
Adenosine A <sub>2B</sub> receptor	1
Adenosine deaminase	1
Adenosine receptor	1
ADORA <sub>2A</sub>	2
Adora <sub>2B</sub>	1
ADRB2	5,10
Adrenergic receptor β <sub>2</sub>	5,10
ALT313	3
ALT844	3
ALT1222	3
AMD3100	8
Apadenoson	3
APOE	8
Apolipoprotein E	8
ARRB2	5
Arrestin β2	5
ATP	3
Auranofin	10
<b>B</b>	
β-Hemoglobin	1
<i>Bacillus anthracis</i> lethal toxin	10
Benzothiazin-4-one	9
Bevirimat dimeglumine	10
<b>C</b>	
Cadherin-5	5
Catena	10
Catenin (cadherin-associated protein) δ1	5
CBP	11
CD62E	2
CD62L	2
CD62P	2
CD144	5
CellSearch System	4
Chemokine CXC motif ligand 10	15
Cholesterol	11
CP-690,550	13
CREB binding protein	11
CREBBP	11
CREB transcription factor	11
CTNND1	5
CXC chemokine receptor 4	8
CXCL10	15

CXCR4	8
Cyclophilin A	8
CYPA	8
<b>D</b>	
<i>Dmd</i>	6
DOR	12
DT1133	3
<i>Dystrophin</i>	6
<b>E</b>	
E selectin	2
<b>F</b>	
FLT1	8
FRAP	12
<b>G</b>	
Glycine transporter type 1	12
GLYT1	12
GMI-1070	2
GSK1018921	12
<b>H</b>	
HBB	1
Histone acetyltransferase	11
HIV capsid protein	10
Hydroxyurea	1
<b>I</b>	
Idebenone	10
Interferon	15
IP-10	15
Isoproterenol	5,10
<b>J</b>	
JAK-3	13
Janus kinase-3	13
<b>L</b>	
LDLR	11
Lexiscan	3
Lipopolysaccharide	11
Lovastatin	11
Low-density lipoprotein receptor	11
LPS	11
L selectin	2
LT	10
<b>M</b>	
μ-Opioid receptor	12
Macrophage migration inhibitory factor	9
Macroporous ferrogel	14
Mammalian target of rapamycin	12
<i>Mdx</i>	6
MicroRNA-499	9
MIF	9
miR-499	9
Mitoxantrone	14
MLL2	8
MLL3	8
MOR	12
Mozobil	8
mTOR	12
<i>mTR</i>	6
Myeloid/lymphoid or mixed-lineage leukemia 2	8
<b>N</b>	
NPY3R	8

<b>O</b>	
Opioid receptor-δ1	12
OPRD1	12
OPRM1	12
Org 25935	12
<b>P</b>	
P2RY6	11
P2Y6	11
p16	7
p53	15
p120	5
PAB1115	1
PEG-ADA	1
Phorbol myristate acetate	9
Pilin	5
PKC	9
Plerixafor	8
PPIA	8
Protein kinase C	9
P selectin	2
Purinergic receptor P2Y G protein-coupled 6	11
Pyrrrolopyrimidine	15
<b>R</b>	
R1678	12
RAFT1	12
Rapamune	12
Rapamycin	12
Regadenoson	3
Ribavirin	15
Ridaura	10
<b>S</b>	
SELE	2
Selectin	2
SELL	2
SELP	2
<i>SHH</i>	14
Sirolimus	12
<i>Sonic hedgehog homolog</i>	14
Stedivaze	3
<b>T</b>	
Tasocitinib	13
<i>Telomerase RNA component</i>	6
<i>Terc</i>	6
TGFBR2	13
TGFβ-RII	13
TP53	15
TPSB2	10
Transferrin	14
Transforming growth factor-β receptor II	13
Tryptase β2	10
Tumor protein p53	15
Type IV pili	5
<b>V</b>	
VE-cadherin	5
VEGF	8
VEGFR-1	8
VEGF receptor 1	8
VX-509	13
<b>W</b>	
<i>Wingless-type MMTV integration site</i>	14
<i>WNT</i>	14