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# BBB-conquering antibodies

By *Benjamin Boettner, Associate Editor*

**Roche** has developed a new transferrin receptor–targeting strategy that dramatically increased delivery of an antibody to the brain.<sup>1</sup> The key advance was slimming the technology, dubbed Brain Shuttle, down to a single transferrin receptor–binding antibody fragment. The pharma showed proof of concept in mice by delivering an anti- $\beta$ -amyloid mAb and now needs to adapt the system for primate brains.

The blood brain barrier (BBB) is composed of endothelial cells that allow the passive exchange of smaller, lipophilic molecules between blood and the brain parenchyma but are impermeable to larger, more hydrophobic molecules such as many biologics.

BBB endothelial cells have evolved dedicated, receptor-mediated transcytosis pathways to shuttle larger endogenous molecules such as transferrin and insulin.<sup>2</sup> Because transferrin is one of the few macromolecules able to trek across the BBB, researchers have developed Trojan horse delivery systems that harness transferrin receptor (TfR)-mediated transcytosis to shuttle biologics into the brain.

First-generation Trojan horses typically consisted of an entire TfR-binding antibody fused to a payload—usually a second antibody against a disease-related target. However, the high affinity of the antibody for TfR led to insufficient target engagement in the brains of animals.<sup>3</sup>

In 2011, Roche's **Genentech Inc.** unit took steps toward addressing both drawbacks by lowering the affinity of a TfR-directed antibody. The result was improved brain uptake.

Genentech then eliminated the need to fuse two antibodies together by developing a bispecific, chimeric antibody. One antigen-binding site was specific for TfR and the other for  $\beta$ -site APP-cleaving enzyme 1 (BACE1), an enzyme that contributes to processing the amyloid precursor protein (APP) into toxic, amyloidogenic forms.

The bispecific antibody achieved brain concentrations of about 20 nM, which was up to 10-fold more than a monospecific, BACE1-directed antibody, and reduced  $\beta$ -amyloid (A $\beta$ ) levels in a mouse model of Alzheimer's disease (AD).<sup>4</sup>

Now, the Roche team, led by Per-Ola Freskgård and Anirvan Ghosh, has taken a different approach. The group took a therapeutic antibody called gantenerumab and fused a TfR-specific antibody fragment to one (monovalent) or both (bivalent) of gantenerumab's heavy chains.

Freskgård is vice director and senior leader for neuroscience at the Roche Pharma Research and Early Development (pRED) section, and Ghosh is head of neuroscience discovery at pRED. Gantenerumab, a HuCAL (Human Combinatorial Antibody Library)-derived mAb

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targeting A $\beta$ , is partnered with **MorphoSys AG** and is in Phase II/III testing to treat AD.

The monovalent version produced the better results—it was efficiently transcytosed via TfRs across the BBB.

In a mouse model of AD, i.v. injections of the monovalent, TfR-binding antibody resulted in 50-fold increased target engagement in amyloid plaques in the brain compared with gantenerumab. The monovalent antibody markedly reduced plaque burden in the animals' cortex and hippocampal brain regions.

The findings were published in *Neuron*.

“The most important finding is that endothelial cells at the BBB differentially process internalized TfR in response to monovalent versus bivalent binding of the receptor. Monovalent binding was preferentially associated with transcytosis, while bivalent binding preferentially led to lysosomal compartmentalization,” said David Hilbert, CSO of cancer antibody company **Zyngenia Inc.** “This will have important consequences for the further development of brain shuttles.”

Richard Daneman, a fellow at the **University of California, San Francisco**, added, “One of the nice things in the new monovalent configuration is that it can be used easily with other therapeutic antibodies. It represents more of a platform than other Trojan horse antibodies.”

The reason, he said, is that the new Brain Shuttle technology incorporates therapeutic antibodies “with their native architecture.”

“In principle, such an efficient brain shuttle can revolutionize the development of medication for neurological disorders,” said Bart De Strooper, a professor at the **Catholic University Leuven** and head of the Department of Molecular and Developmental Genetics at the **Flanders Institute for Biotechnology (VIB)**.

**Shuttle service**

Roche is already testing its Brain Shuttle technology in combination with at least two therapeutic modalities—antisense and antibodies.

Under a 2013 deal with **Isis Pharmaceuticals Inc.**, the partners are combining Brain Shuttle with antisense molecules against huntingtin (HTT) protein to treat Huntington's disease (HD).

Also last year, Roche partnered with **Prothena Corp. plc** to develop a Brain Shuttle version of a mAb from the biotech to treat Parkinson's disease (PD).

Regardless of modality, De Strooper wanted to see more *in vivo* toxicity testing of Brain Shuttle in chronic conditions.

“TfR-specific antibodies can cause severe problems with red blood cells,” he noted.

For example, anti-TfR antibodies are associated with defects in reticulocytes, immature red blood cells that express high levels of the receptor required to take up transferrin-bound iron needed for hemoglobin loading and cell maturation.<sup>5</sup>

Earlier this week, the Genentech team published data showing how high-affinity, TfR-directed antibodies such as its TfR-BACE1 bispecific, chimeric antibody drive TfR into the lysosome for degradation. Over time, TfR levels become depleted, rendering the pathway unavailable for transcytosis of endogenous molecules and biologics.<sup>6</sup>

In contrast, Roche's monovalent TfR format could avoid toxicity because it preserved normal TfR levels on the luminal side of the BBB and did not induce TfR degradation in mice.

Michael Ehlers, SVP and CSO of the neuroscience research unit at **Pfizer Inc.**, wanted to see more characterization of Brain Shuttle. “So far the distribution of the antibody has only been assessed by immunofluorescence-based signal amplification,” he said. “It will be important to assess the antibody fraction that reaches the brain parenchyma more directly at higher resolution in time course experiments and to investigate where and how long it is detectable.”

Hilbert thinks that affinity and valency are “two sides of the same coin” and that further work will help to define the role of each in transcytosis. It would be interesting to test Brain Shuttle and Genentech’s approach head to head. “True affinities of the Trojan horse antibodies

by Genentech and Roche still need to be measured by more sensitive means such as surface plasmon resonance,” he said.

“It would make sense and be straightforward to compare the different TfR-based Trojan horse shuttles side by side and quantify their effective brain concentrations. *In vivo* assays

could be used to further translate such results,” added Ehlers.

Moreover, he said that “more experiments should be done in wild-type animals since mouse models of AD often have impaired vascular integrity.” Indeed, A $\beta$  forms aggregates in the cerebrovasculature that can locally disrupt the BBB.

### Deciphering the human BBB

Freskgård said that Roche is now pushing ahead with plans to generate Brain Shuttle modules with primate and human TfRs.

Daneman said that primate- or human-specific anti-TfR antibodies will likely have varying binding affinities and TfR functions.

“The BBB and the functions of individual transport systems like TfRs likely differ between rodents and primates so that efficacy seen in rodent

models cannot necessarily be anticipated in humans. Therefore, a more detailed understanding about the BBB in primates will be very useful,” said Ehlers.

He said that a team at the **University of Wisconsin–Madison** is developing human induced pluripotent stem (iPS) cell protocols that generate *in vitro* systems able to recapitulate aspects of the human BBB.<sup>7</sup>

Roche’s pRED has filed a patent application covering BBB transport using the monovalent Brain Shuttle module. The IP is not available for licensing.

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### COMPANIES AND INSTITUTIONS MENTIONED

**Catholic University Leuven**, Leuven, Belgium  
**Flanders Institute for Biotechnology**, Leuven, Belgium  
**Genentech Inc.**, South San Francisco, Calif.  
**Isis Pharmaceuticals Inc.** (NASDAQ:ISIS), Carlsbad, Calif.  
**MorphoSys AG** (Xetra:MOR; Pink:MPSYF), Martinsried, Germany  
**Pfizer Inc.** (NYSE:PFE), New York, N.Y.  
**Prothena Corp. plc** (NASDAQ:PRTA), Dublin, Ireland  
**Roche** (SIX:ROG; OTCQX:RHHBY), Basel, Switzerland  
**University of California, San Francisco**, Calif.  
**University of Wisconsin–Madison**, Madison, Wis.  
**Zyngenia Inc.**, Gaithersburg, Md.

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# Translational tidbits

By Lev Osherovich, Senior Writer

## Amgen's IBD gene hunt

**Amgen Inc.** is teaming up with researchers at **Massachusetts General Hospital** and the **Broad Institute of MIT and Harvard** to find new targets in inflammatory bowel disease. The partners hope an unbiased search for genetic variants that lower risk of the autoimmune disorder will uncover therapeutic entry points.

Amgen will work with teams led by Ramnik Xavier, chief of gastroenterology and director of the Center for the Study of Inflammatory Bowel Disease at MGH, and Mark Daly, an associate professor of medicine at MGH. Xavier and Daly are both senior associate members of the Broad Institute.

Inflammatory bowel disease (IBD) encompasses Crohn's disease and ulcerative colitis (UC). Genetic and tissue studies have implicated a diverse range of immunological, metabolic and gut microbial pathways in IBD.

Prior genomewide association studies by Xavier and others have identified genetic variants that strongly influence IBD risk.<sup>1</sup> However, not everyone carrying these risk genes becomes ill. Thus, Xavier suspects that additional, unknown genetic factors can counteract disease-associated genes and protect against IBD.

"The aim of the collaboration is to find these protective variants," said Xavier. "We will look at individuals who have not yet developed disease despite having genetic variants associated with high risk."

The team will use computational methods developed by Daly's team to re-analyze existing genomewide association data to tease out putative protective genes.

Xavier said that the work plan first involves identifying the protective genes, then categorizing them into functional categories and testing their effect in tissue culture models of IBD.

The collaborators will use materials from the Prospective Registry in IBD Study at MGH (PRISM), which stores pre- and post-treatment biopsy and fecal samples from several hundred patients with IBD.

Sasha Kamb, SVP of discovery research at Amgen, said that the project is a fishing expedition to survey the landscape of IBD genetics for potential targets. He said that the ideal target would be a druggable protein encoded by an IBD risk-reducing variant that has lower function than the wild-type protein.

"We are interested in protection against disease caused by reduced function of a gene," said Kamb. "The big win would be a relatively illuminated path to a therapeutic that starts from a protective drug target."

Kamb said that one of the biggest challenges to understanding the causes of IBD is variation in the interplay between immune activity and intestinal microbiota.

"IBD is immensely complicated, involving interactions between the immune system and the gut," said Kamb. "Host-commensal organism interactions potentially create a lot of heterogeneity between patients."

Indeed, Kamb and Xavier suspect that no two patients are likely to have exactly the same genetic and microbial risk factors and that the etiologies of IBD may prove to be highly individual.

"What is emerging is that there are many types of Crohn's disease and ulcerative colitis," said Xavier.

Financial details of the partnership are undisclosed. Amgen will gain undisclosed rights to IP arising from the collaboration.

Amgen's AMG 181, a mAb that prevents integrin  $\alpha_4\beta_7$ , from binding to mucosal vascular addressin cell adhesion molecule 1 (MAdCAM-1), is in Phase II testing for Crohn's disease.

In 2012, Amgen acquired deCode genetics ehf, an Icelandic genetics company. Although deCode's researchers have previously reported genetic studies of IBD, Kamb said that the Broad collaboration will operate independently of deCode.

## Lakeside drug shop

Two European drug discovery centers and an Italian CRO have partnered to launch a drug screening center at a shuttered pharma facility in Constance, Germany.

The new center—**Hit Discovery Constance GmbH** (HDC)—is a joint venture between the Dortmund-based **Lead Discovery Center GmbH** (LDC), the **Centre for Drug Design and Discovery** (CD3) in Leuven and Milan's **Axxam S.p.A.** HDC is based at a screening facility previously operated by Nycomed, which was acquired by **Takeda Pharmaceutical Co. Ltd.**

LDC is a discovery service provider spun out of **Max Planck Innovation GmbH**, the technology transfer arm of Germany's **Max Planck Society**. CD3 was set up by Belgium's **Catholic University Leuven** and the **European Investment Fund** to perform drug discovery for academic laboratories and small, regional biotechs.

"LDC had the means to run a small screening center, but we often had to rely on CROs to do assay adaptation and high throughput screening for assays with sophisticated read-out formats," said Thomas Hegendörfer, head of business development at LDC.

Hegendörfer said that LDC had previously collaborated on drug screen projects at the former Nycomed facility and wished to continue using it.

"When it became clear that Takeda was going to close it down and lay off the people, we were thinking about how to continue with access," said Hegendörfer. "We negotiated with Takeda about acquiring the entire lab" on undisclosed terms.

Having HDC operational "opens up additional possibilities to do more sophisticated screens such as with radiometric formats and high content screening under biological safety regulations," said Stefaan Allemeersch, director of business development for CD3 and managing director at HDC.

Hegendörfer said that Axxam came on board to expand the range of screening technologies for its commercial screening business.

"We had previously used Axxam as a screening partner for ion channels and GPCRs," said Hegendörfer. "This gives them additional opportunities in the service field."

Hegendörfer and Allemeersch said that HDC will primarily provide screening services for academic clients recruited by CD3 and LDC. HDC's team of five people is already working on two such projects.

Details about how shares in HDC are divided among the three stakeholders were not disclosed.

## Public-private partnership roundup

In December, the **New York City Economic Development Corp.** launched its Early-Stage Life Sciences Funding Initiative with partners **Celgene Corp.**, **Eli Lilly and Co.** and **General Electric Co.** to drive newco

**Table 1. Selected public-private partnerships for December 2013.** Public-private partnership activity ebbed as the year drew to a close. The number of notable deals in December came in at 17, dipping below 20 for the first time since July.

Source: BioCentury Archives

Companies	Institutions	Business area	Disclosed value	Purpose
<b>Celgene Corp.</b> (NASDAQ:CELG); <b>Eli Lilly and Co.</b> (NYSE:LLY); <b>General Electric Co.</b> (NYSE:GE)	<b>New York City Economic Development Corp.</b>	Other	At least \$100 million	City of New York Early-Stage Life Sciences Funding Initiative to invest at least \$100 million in early stage life science companies in the city
Not applicable	<b>Agency for Innovation by Science and Technology; Austrian Science Fund; Danish Agency for Science, Technology and Innovation; The French National Research Agency; The Foundation for Science and Technology; Hungarian Academy of Sciences; Hungarian Scientific Research Fund; Ministry of Economy and Competitiveness; National Authority for Scientific Research; The National Centre for Research and Development; National Science Centre; Project Management Julich; Office of the Chief Scientist; Institute of Health Carlos III; European Commission</b>	Infectious disease	€9.2 million (\$12.7 million)	Infect-ERA consortium to coordinate research projects on infectious diseases
<b>Cardio3 BioSciences S.A.</b> (Euronext:CARD); <b>AdjuCor GmbH; Boston Scientific Corp.</b> (NYSE:BSX); <b>Contipro Biotech s.r.o.; Explora Biotech s.r.l.; Innova S.p.A.</b>	<b>Eberhard Karls University of Tuebingen; Fraunhofer Institute for Interfacial Engineering and Biotechnology; Royal College of Surgeons in Ireland; Trinity College Dublin; European Commission</b>	Cardiovascular disease	€8.7 million (\$11.8 million)	Advanced Materials for Cardiac Regeneration (AMCARE) consortium to develop a bioresorbable polymeric valve tube to treat congenital heart defects
<b>AstraZeneca plc</b> (LSE:AZN; NYSE:AZN)	<b>The Johns Hopkins University</b>	Pharmaceuticals	\$6.5 million	Collaboration to focus on research projects in <b>MedImmune LLC</b> unit's therapeutic areas of interest
<b>Eisai Co. Ltd.</b> (Tokyo:4523); <b>Eli Lilly</b>	<b>Alzheimer's Research UK; MRC Technology</b>	Neurology	£3 million (\$4.9 million)	Dementia consortium to develop drug targets from academic sources
<b>Sareum Holdings plc</b> (LSE:SAR)	<b>Hebei Medical University Biomedical Engineering Center</b>	Cancer	Undisclosed	Co-development agreement for Sareum's inhibitor of aurora kinases and FMS-like tyrosine kinase 3 (FLT3; CD135)
<b>GlaxoSmithKline plc</b> (LSE:GSK; NYSE:GSK)	<b>Gustave Roussy Institute; Memorial Sloan-Kettering Cancer Center; Netherlands Cancer Institute; Princess Margaret Cancer Centre; The University of Texas MD Anderson Cancer Center; Vall d'Hebron Institute of Oncology</b>	Cancer	Unavailable	Oncology Clinical and Translational Consortium (OCTC) to conduct Phase I/II single-agent and combination trials with GSK's early stage cancer pipeline
<b>Amgen Inc.</b> (NASDAQ:AMGN)	<b>International Myeloma Foundation</b>	Cancer	Undisclosed	Partnership to support foundation's Black Swan Research Initiative that aims to define and assess minimal residual disease (MRD) as a clinical endpoint
<b>Ariana Pharma; Bruker Corp.</b> (NASDAQ:BRKR)	<b>University Hospitals of Strasbourg; University of Strasbourg</b>	Cancer; Diagnostics	Unavailable	ExtempoNMR project to develop a tool for <i>in vitro</i> cancerous tissue diagnosis during surgical procedures
<b>AstraZeneca; Cancer Research Technology Ltd.</b>	<b>Cancer Research UK</b>	Cancer	Undisclosed	Partnership to develop the CC chemokine receptor 4 (CCR4; CD194) antagonist AZD2098 for kidney cancer
<b>Cellular Dynamics International Inc.</b> (NASDAQ:ICEL)	<b>The Hamner Institutes for Health Sciences</b>	Diagnostics	Undisclosed	Partnership to develop predictive <i>in vitro</i> screening assays for chemical, environmental and pharmaceutical toxicology assessments

(Continues on p. 6)

**Table 1. Selected public-private partnerships for December 2013.** (continued)

Companies	Institutions	Business area	Disclosed value	Purpose
Domain Therapeutics S.A.	McGill University; University of Montreal	Diagnostics	Undisclosed	Partnership to develop biosensors using GPCR technology created at University of Montreal
Johnson & Johnson (NYSE:JNJ)	Neomed Institute	Pharmaceuticals; Diagnostics	Unavailable	Partnership to jointly identify and fund early stage life science technologies from Neomed's academic and biotech partners
Merck & Co. Inc. (NYSE:MRK)	Not applicable	Pharmaceuticals	Undisclosed	Plan to create four innovation hubs to identify external early stage and late-stage R&D opportunities that the pharma could license or acquire
Neurimmune Therapeutics AG; Anelixis Therapeutics LLC	ALS Therapy Development Institute	Neurology	Undisclosed	Partnership to develop preclinical human antibodies from Neurimmune that target misfolded superoxide dismutase 1 (SOD1) to treat amyotrophic lateral sclerosis (ALS)
Not applicable	Harvard University; U.S. Army Research, Development and Engineering Command	Diagnostics	Unavailable	Partnership to advance organ-on-a-chip research to improve chemical and biological testing
Novogen Ltd. (ASX:NRT; NASDAQ:NVGN)	Weill Cornell Medical College	Cancer	Undisclosed	Partnership to develop trilexium to treat glioblastoma multiforme (GBM)

formation in the city. The initiative will create a VC-managed fund to invest at least \$100 million in 15–20 early stage life science companies by 2020 (see Table 1, “Selected public-private partnerships for December 2013”).

**Johnson & Johnson's** Johnson & Johnson Innovation LLC and Janssen Labs units continued to expand into Canada by teaming up with the **Neomed Institute** to jointly identify and fund early stage life science technologies from Neomed's academic and biotech partners.

The deal follows a similar November collaboration in which J&J Innovation and Janssen partnered with Canada's **MaRS Innovation** to jointly identify and fund early stage life science technologies from MaRS's 16 member institutions.

Meanwhile, **Merck & Co. Inc.** is picking up the innovation center model by creating four innovation hubs in or near Boston, San Francisco, London and Shanghai. The hubs will identify external early stage and late-stage R&D opportunities that the pharma could license or acquire.

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## COMPANIES AND INSTITUTIONS MENTIONED

**Amgen Inc.** (NASDAQ:AMGN), Thousand Oaks, Calif.  
**Axxam S.p.A.**, Milan, Italy  
**Broad Institute of MIT and Harvard**, Cambridge, Mass.  
**Catholic University Leuven**, Leuven, Belgium  
**Celgene Corp.** (NASDAQ:CELG), Summit, N.J.  
**Centre for Drug Design and Discovery**, Leuven, Belgium  
**Eli Lilly and Co.** (NYSE:LLY), Indianapolis, Ind.  
**European Investment Fund**, Luxemburg City, Luxembourg  
**General Electric Co.** (NYSE:GE), Fairfield, Conn.  
**Hit Discovery Constance GmbH**, Constance, Germany  
**Johnson & Johnson** (NYSE:JNJ), New Brunswick, N.J.  
**Lead Discovery Center GmbH**, Dortmund, Germany  
**MaRS Innovation**, Toronto, Ontario, Canada  
**Massachusetts General Hospital**, Boston, Mass.  
**Max Planck Innovation GmbH**, Munich, Germany  
**Max Planck Society**, Munich, Germany  
**Merck & Co. Inc.** (NYSE:MRK), Whitehouse Station, N.J.  
**Neomed Institute**, Montreal, Quebec, Canada  
**New York City Economic Development Corp.**, New York, N.Y.  
**Takeda Pharmaceutical Co. Ltd.** (Tokyo:4502), Osaka, Japan

# NCATS two years later

By C. Simone Fishburn, Senior Editor

The **National Center for Advancing Translational Sciences** (NCATS) was founded at the NIH a little over two years ago, in the wake of increasing concern over the slow pace of converting scientific discoveries into new therapies. “*BioCentury This Week*” television sat down with NCATS director Christopher Austin to discuss how NCATS is delivering on its promise to overcome the roadblocks and accelerate the translational process.

Austin thinks that NCATS’s biggest advantage is its ability to collaborate with different players in the field to fill gaps left underdeveloped by industry and academia. Examples include the Tissue Chip for Drug Screening program and the New Therapeutic Uses program.

The former is a collaboration between the NIH, **FDA** and **Defense Advanced Research Projects Agency** (DARPA) that aims to develop 3D human tissue chips that model human organs for use in predicting toxic effects of candidate therapeutics, as discussed by DARPA’s Jay Schnitzer on “*BioCentury This Week*.”

The New Therapeutic Uses program provides a channel between pharma and the biomedical research community to help repurpose compounds not pursued for their original indication for scientific or commercial reasons.<sup>1</sup>

Austin also pointed to new interventions in Parkinson’s disease (PD) that might arise from a joint genomewide siRNA screen performed by NCATS scientists and researchers from the **National Institute of Neurological Disorders and Stroke** and the **NIH Center for Regenerative Medicine**.

Results of the screen, which were published in *Nature*, identified proteins that regulate the accumulation of parkin (PARK2) in mitochondria, a process that has recently come to the forefront of PD research.<sup>2</sup>

NCATS also wants to play a role in areas in which the private sector sees too much risk. For example, the Therapeutics for Rare and Neglected Diseases (TRND) program at NCATS brings not-for-profit organizations together with academic and industry partners to enable preclinical testing of compounds for under-served diseases.

Edited excerpts from the *BioCentury This Week* television (BCTV) interview with Austin follow.

**BCTV:** NCATS’s mission is to re-engineer the way basic research is translated into medicine. Supporters say NCATS will solve problems academics and industry can’t tackle on their own, but skeptics inside academia and industry and even at NIH say it diverts funds from NIH’s core research mission and is taking on tasks that should be left to drug companies.

Let’s start with target validation, which is one of the things that NCATS is looking to improve. That’s what many drug companies exist to do. So why do we need NCATS to do it?

**Christopher Austin:** Right. Thanks to the Genome Project, among other things, there are many more targets than we can possibly deal with. For

example, there are about 6,000 rare diseases, and we now know, from the Genome Project and other advances, the genetic basis of about 4,000 of them. That’s up from 50 about 15 or 20 years ago.

So although there are thousands of putative targets that could be investigated, we don’t have very good ways of sifting through the data to identify the targets that are the most tractable.

We believe the solution lies in one of the core principles of NCATS, which is that translation is a team sport.

Early on in the science process, it can be a fairly solitary exercise. That’s how I got my start in fundamental genetics research, but translation requires multiple players with distinct expertise from multiple disciplines and multiple organizations. Every project NCATS does is a collaboration with somebody in the public sector or the private sector, so we are not doing this alone.

**BCTV:** And can you give examples of outcomes or of how NCATS can deliver real results?

**CA:** The NCATS RNAi program is focused on the general principles that underlie using RNAi as a target validation tool. We started by using genomewide RNAi to knock out every gene one by one and find every gene involved in disease or a cellular process—and thereby identify targets.

But the RNAi technology initially was not usable for that use, so our people developed new technologies to allow that to happen.

There was no public database, so researchers around the world had no access to the data. And so we developed new screening, informatics and analysis technologies to fix that.

We developed the first public database for these data in collaboration with **Life Technologies Corp.**, and we’ve done a number of projects now on very important diseases to identify novel targets for intervention. One example is the paper we published last month in *Nature* on Parkinson’s disease.

**BCTV:** Another area NCATS is working on is improving the process of getting drugs and new therapies to people who need them—not simply getting them approved, but actually getting them disseminated. Many biotech and pharma companies and academics don’t seem to focus much on that. What are you doing there?

**CA:** This is a very important problem, as part of NCATS’s mission is to improve health. Getting a drug approved can be very important, but we haven’t actually improved health there.

It currently takes between 10 and 15 years to get new medicines approved by FDA to all the patients that need them. And this is a problem

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**— Christopher Austin,  
National Center for Advancing  
Translational Sciences**

that includes reimbursement, patient access to medicine, heterogeneity in the population—genetically and environmentally—and heterogeneity of disease.

*BCTV:* So again—why is this something that NIH needs to do? A drug company has a fantastic incentive to get new drugs used as widely as possible as quickly as possible.

*CA:* We should do it because NCATS is focused on areas where we think we can do things better. As an example, it's well known that most patients who were prescribed a medicine either never fill the prescription or they only take it one month and then they stop.

And so this is an issue of physician behavior, prescribing behavior and patient behavior. And this is an issue of implementation science, which is quite different from the fundamental preclinical work that NCATS does.

Through our CTSA program, the Clinical Translational Science Award program, which is a network of 62 academic medical centers all over the country—it's actually NIH's biggest single program—we have really pushed the idea of patient engagement and community engagement from the very beginning of projects.

One of the reasons that patients do not take the medicines that might be prescribed them is they don't feel that they're partners with their prescribers in understanding what these medicines can do for them. And so they're not invested, and they don't take them.

It's an interesting development that patient groups are becoming much more active in the development and utilization of medicines for diseases. And we think this is a transformational development, and I've actually challenged NCATS to have our people and our grantees and our internal scientists involve patients in every project we do from the very beginning.

*BCTV:* Can you give us some other examples of the way that you've tried to use your funding to meet your goal of transforming medicine—and at \$10 million a year that funding is a lot less than the half-a-billion dollars originally envisioned?

*CA:* We are using the money well; for example, for the Tissue Chip program—a body on a chip to do toxicology—which, if successful, will transform how we identify the safety and efficacy of novel therapeutics.

Another example is in a collaboration we have called New Therapeutic Uses with eight pharmaceutical companies, which addresses the problem that because of a very high failure rate of drug development, for every drug that gets approved for human use by the FDA, there are about 10 which have been in people and then fail, often for efficacy reasons or for business reasons.

We teamed up with these companies and proposed reaching out to the academic community to see if there are other ideas for diseases that these drugs might be used for. By advancing the repurposing of these compounds, there are actually compounds for nine different diseases that are in patients right now in collaboration between NCATS and academic organizations and the pharmaceutical companies who made the drugs and have all the data on them.

I would say it will take about a year to get some results. Some of them are actually getting animal studies done on them, so we'll know a little bit earlier than that.

But I should say that this whole program was about \$13 million, which is a very small amount of money that could catalyze nine new drugs.

*BCTV:* Going back to rare diseases, tell us about the TRND project, which is trying to find new therapies for really rare diseases. What are you working on there, and again why is it something that the private sector, which has invested a lot in rare diseases, wouldn't do on its own?

*CA:* There are many rare diseases that are not sufficiently de-risked for a company to make a business case to adopt them. And the purpose of TRND is to be the starting point of proto-drug development up to a point where a company is willing to adopt them. So it's really an adapter or a chaperone for those projects.

Sickle cell disease is a very important public health disease that affects about 100,000 people in this country. It was the first genetic disease [for which the cause was identified], in 1949. We still have no treatment for that disease based on that genetic discovery.

**AesRx LLC**, a little biotech in Boston, came to us with an unconventional molecule. It's an unconventional mechanism. There have been regulatory issues of getting drugs for sickle cell approved, and there are clinical trial issues in that particular disease, which have bedeviled that disease from the beginning.

No company would adopt that project because of all those risks, despite the very important public health implications. So we adopted that project, working very closely with AesRx, having a joint project team that decided where the funding that NCATS put into it would go. And the company put their own resources into it. And within a year, we went from starting that collaboration to being in people.

So this is what I want to emphasize, is that rapid advances in translation are possible. They weren't possible when I was in training 40 years ago. They are possible now. It's a matter of will and having the science and operational systems to do it.

*BCTV:* Thank you very much.

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**Defense Advanced Research Projects Agency**, Arlington, Va.  
**Food and Drug Administration**, Silver Spring, Md.  
**Life Technologies Corp.** (NASDAQ:LIFE), Carlsbad, Calif.  
**National Center for Advancing Translational Sciences**, Bethesda, Md.  
**National Institute of Neurological Disorders and Stroke**, Bethesda, Md.  
**National Institutes of Health**, Bethesda, Md.  
**NIH Center for Regenerative Medicine**, Bethesda, Md.

# PTSD: rewriting fearful memories

By Michael J. Haas, Senior Writer

A **Massachusetts Institute of Technology**–led team has outlined a strategy for addressing the underlying causes of post-traumatic stress disorder.<sup>1</sup> The approach centers on blocking histone deacetylase 2, which is the only class I histone deacetylase target with a growing body of evidence suggesting a role in learning and memory.

Future studies will need to identify a selective histone deacetylase 2 (HDAC2) inhibitor and determine its optimal human dosing to avoid unwanted effects on memory.

Post-traumatic stress disorder (PTSD) is caused by a traumatizing event that the individual re-experiences episodically when environmental or situational cues trigger its recollection. Approved PTSD drugs help manage the anxiety associated with the traumatic memory and include antidepressants or anxiolytics, sometimes in combination with atypical antipsychotics.

Behavioral approaches include exposing the patient to the trauma-associated cues in a safe setting. This allows the patient to reinterpret those cues as neutral and thus develop reduced anxiety responses to them—a process known as extinction.

Neither drugs nor behavior therapy alters the underlying memory of the original trauma that triggers PTSD episodes. Moreover, patients may be averse to recalling the traumatic event and thus may not complete the series of exposure therapy sessions needed for extinction.

Over the past seven years, multiple groups have shown that inhibitors of class I HDACs improved the effectiveness of extinction protocols in fear-conditioned mice when given a day after the completion of fear conditioning.<sup>2-7</sup>

These studies did not examine the effect of combining class I HDAC inhibition and extinction protocols in mice several days or weeks after fear conditioning—an approach that would more closely model human PTSD.

Thus, the role of class I HDACs in the extinction of anxiety responses to long-term traumatic memories was poorly understood.

That began to change in 2009 and 2012 when teams led by Li-Huei Tsai showed that HDAC2—but not other class I HDACs—blocked memory formation in mice<sup>8</sup> and contributed to long-term memory impairment in patients with Alzheimer's disease (AD).<sup>9</sup>

Also in those studies, Hdac2 reduced memory deficits in the normal mice and mouse models of AD.

Tsai told *SciBX* that those studies led her to speculate that inhibiting HDAC2 might have a therapeutic effect on long-term memories in fear-conditioned mouse models of PTSD.

For the recent study, Tsai's new team first compared the effectiveness of extinction protocols in mice one day after fear conditioning (recent

memory models) and one month after fear conditioning (remote memory models).

Initially, extinction protocols were effective at eliminating conditioned fear responses in both PTSD models. Over time, however, only the remote memory models exhibited spontaneous recovery of the fear response, thus demonstrating that the extinction protocols could not completely eliminate long-term fear memories.

The fear-memory recall triggered by the extinction protocols was accompanied by elevated Hdac2-chromatin dissociation and a consequent reduction of Hdac2 activity in the hippocampal neurons of the recent memory models—but not in the neurons of the remote memory models. Moreover, the duration of the reduction in Hdac2 activity in the recent memory models coincided with the reconsolidation window, a six-hour period in mice during which a recalled memory can be altered or rewritten.<sup>10</sup>

These results suggested that extinction therapy was not completely effective in the remote memory models because the retention of hippocampal Hdac2 activity following fear-memory recall made the memory resistant to alteration. Indeed, the team showed that in the remote memory models undergoing the extinction protocol, Hdac2 blockade with a CNS-penetrating research compound that inhibited class I HDACs

during the six-hour reconsolidation window decreased the conditioned fear response and spontaneous recovery of that response and increased the synaptic and structural plasticity of hippocampal neurons compared with no Hdac2 blockade.

Taken together, the results suggest that inhibition of HDAC2 could improve the ability of extinction therapies to rewrite the long-term traumatic memories that underlie PTSD, the team wrote in its report in *Cell*.

Tsai is director of the Picower Institute for Learning and Memory and a professor of neuroscience at the Massachusetts Institute of

Technology (MIT). She is also a senior associate member at the **Broad Institute of MIT and Harvard**.

Her team included researchers from the **Massachusetts General Hospital, Harvard Medical School, the Howard Hughes Medical Institute** and the **Washington University in St. Louis School of Medicine**.

“This study is important because it shows that an old memory of fear can be successfully extinguished and spontaneous recovery of fear memory—which can occur in PTSD patients—can be abolished as well,” said Yossef Itzhak, a professor of psychiatry and behavioral sciences and of molecular and cellular pharmacology at the **University of Miami Miller School of Medicine**.

The HDAC2 inhibitor “induced epigenetic changes that shaped the brain to be more responsive to changes in behavior,” he said.

“That’s what’s exciting to us about the therapeutic strategy in the *Cell* paper,” added Martin Jefson, CSO of **Rodin Therapeutics Inc.** and an entrepreneur in residence at **Atlas Venture**. “It takes advantage of the cognitive flexibility that occurs when memory is recalled and provides an opportunity to alter the expression of genes associated with formation of

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University of Miami Miller  
School of Medicine**

synapses and memory—thus breaking the association between fear and the recalled memory.”

K. Matthew Lattal, an associate professor of behavioral neuroscience at **Oregon Health & Science University**, agreed. The ability of an HDAC2 inhibitor to potentially promote memory formation at the molecular level “could strengthen the patient’s perception that the memories previously associated with trauma have become safe” as a result of exposure therapy, he said. The combination of HDAC2 inhibition and exposure therapy may “result in the long-term suppression of the traumatic memory and increase the likelihood that the treatment will have a long-term impact.”

He said that an important feature of the study was the long interval of time between fear conditioning and the combined HDAC2 inhibition–extinction therapy. “This may provide a more effective way to model human PTSD because treatment in patients often does not occur until well after the traumatic experience,” Lattal told *SciBX*.

### Selectively fearless

Jefson said that the findings are ready for clinical testing. “There’s not much more to be explored here preclinically. PTSD is a complex human behavior, and it’s not adequately modeled in animals,” he noted.

Ankit Mahadevia, acting CBO of Rodin and a venture partner at Atlas, agreed, noting that the real challenge will be identifying a selective HDAC2 inhibitor.

Indeed, most of the safety issues associated with HDAC inhibitors arise from their nonselectivity for individual HDACs, Jefson said. As examples, he cited preclinical studies showing that double knockout of *Hdac2* and *Hdac1* in mice resulted in anemia, thrombocytopenia, peripheral nervous system and CNS abnormalities, cardiomyopathies and other pathologies not observed in single-knockout mice.<sup>11,12</sup>

There are two nonselective HDAC inhibitors on the market—Istodax romidepsin and Zolinda vorinostat. Istodax’s side effects include nausea, fatigue, thrombocytopenia, anemia and electrocardiographic changes, whereas the side effects of Zolinda include nausea, diarrhea, fatigue, thrombocytopenia and anorexia.

**Celgene Corp.** markets Istodax to treat cutaneous T cell lymphoma (CTCL) and lymphoma. **Merck & Co. Inc.** and **Taiho Pharmaceutical Co. Ltd.** market Zolinda to treat CTCL.

“It will be important to identify specific inhibitors of HDAC2 that target only the brain circuits and genes” involved in memory, said Itzhak.

“Good selectivity in an HDAC2 inhibitor would thus provide a wide therapeutic index for PTSD and open the door to using the inhibitor in other conditions where it could enhance cognition,” such as AD, phobia and cognitive impairment in schizophrenia, Mahadevia said.

“Selectivity of the inhibitor would also be important because there is still a lot to be worked out about how it would be dosed in humans,” added Mahadevia. “We don’t know yet whether a patient would need to be exposed to the inhibitor periodically, acutely or chronically” to achieve the desired effect on rewriting fear memories in patients with PTSD.

Lattal cautioned that dosing and duration of HDAC2 inhibition will have to coincide closely with the exposure therapy session to avoid inducing new, potentially detrimental associations in the patient.

“For example, let’s say you have a recovering alcoholic who is on an HDAC2 inhibitor to treat PTSD and he experiences an episodic relapse in his alcoholism,” he said. If that patient walks into a bar for a drink while the inhibitor is in his system, the result could be “a strengthened association between the bar environment and the positive intoxication state—meaning that an unintentional side effect of the inhibitor could be an increased probability of another relapse” in his alcoholism.

Rodin is developing selective HDAC inhibitors but has not disclosed details about its pipeline, including specific targets or indications.

Tsai is a member of Rodin’s scientific advisory board, but Mahadevia declined to disclose whether the company would in-license the findings her team reported in *Cell*. But he added, “We have composition of matter around selective HDAC inhibitors that we could use to explore these findings.”

Tsai said that her team’s planned work includes looking for other targets that play roles in cognitive function and could be targeted with small molecules.

She said that the findings reported in *Cell* are covered by both issued patents and patent applications owned and filed by MIT, and the IP is available for licensing.

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### COMPANIES AND INSTITUTIONS MENTIONED

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**Broad Institute of MIT and Harvard**, Cambridge, Mass.  
**Celgene Corp.** (NASDAQ:CELG), Summit, N.J.  
**Harvard Medical School**, Boston, Mass.  
**Howard Hughes Medical Institute**, Chevy Chase, Md.  
**Massachusetts General Hospital**, Boston, Mass.  
**Massachusetts Institute of Technology**, Cambridge, Mass.  
**Merck & Co. Inc.** (NYSE:MRK), Whitehouse Station, N.J.  
**Oregon Health & Science University**, Portland, Ore.  
**Rodin Therapeutics Inc.**, Cambridge, Mass.  
**Taiho Pharmaceutical Co. Ltd.**, Tokyo, Japan  
**University of Miami Miller School of Medicine**, Miami, Fla.  
**Washington University in St. Louis School of Medicine**, St. Louis, Mo.

## 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>Autoimmune disease</b>				
Arthritis	$\beta$ -Glucuronidase (GUSB)	<p>Mouse studies suggest stimulating GUSB activity could help protect against Lyme disease-associated arthritis. A partial loss-of-function variant of <i>Gusb</i> was found in mouse strains highly susceptible to severe arthritis following <i>Borrelia burgdorferi</i> infection but not in mice with lower susceptibility. In mice with the <i>Gusb</i> variant, overexpression of wild-type <i>Gusb</i> decreased <i>B. burgdorferi</i>-induced arthritis compared with normal expression. In mice with severe <i>B. burgdorferi</i>-induced arthritis, inflammatory glycosaminoglycans, which are degraded by <i>Gusb</i>, accumulated in joint tissues. Next steps could include study of GUSB or glycosaminoglycans as biomarkers of human susceptibility to arthritis.</p> <p><b>SciBX 7(4); doi:10.1038/scibx.2014.108</b> Published online Jan. 30, 2014</p>	Unpatented; licensing status not applicable	<p>Bramwell, K.C. <i>et al. J. Clin. Invest.</i>; published online Dec. 16, 2013; doi:10.1172/JCI72339  <b>Contact:</b> Janis J. Weis, University of Utah School of Medicine, Salt Lake City, Utah            e-mail: <a href="mailto:janis.weis@path.utah.edu">janis.weis@path.utah.edu</a></p>
Psoriasis	B and T lymphocyte attenuator (BTLA)	<p>Cell culture and mouse studies suggest agonizing BTLA could help treat psoriasis. In a subset of cultured <math>\gamma\delta</math> T cells treated with Il-7, <i>Btla</i> knockout cells showed greater proinflammatory Il-17 and tumor necrosis factor (TNF) production than wild-type cells. In a mouse model of acute dermatitis, <i>Btla</i> knockout mice had more severe inflammation than wild-type mice. In wild-type mice with acute dermatitis, an antibody that agonizes <i>Btla</i> decreased epidermal thickening compared with no treatment. Next steps in collaboration with Pfizer Inc.'s Center for Therapeutic Innovation include targeting BTLA with its ligand, tumor necrosis factor receptor superfamily member 14 (HVEM; TNFRSF14; LIGHTR).</p> <p><b>SciBX 7(4); doi:10.1038/scibx.2014.109</b> Published online Jan. 30, 2014</p>	Patent and licensing status undisclosed	<p>Bekiaris, V. <i>et al. Immunity</i>; published online Dec. 5, 2013; doi:10.1016/j.immuni.2013.10.017  <b>Contact:</b> Carl F. Ware, Sanford-Burnham Medical Research Institute, La Jolla, Calif.            e-mail: <a href="mailto:cware@sanfordburnham.org">cware@sanfordburnham.org</a></p>



## This week in therapeutics (continued)

Indication	Target/marker/pathway	Summary	Licensing status	Publication and contact information
Breast cancer	Homeobox A1 (HOXA1)	<p><i>In vitro</i> and mouse studies suggest depleting <i>HOXA1</i> could prevent progression of early breast cancer lesions. Computational evaluation and comparison of networks of gene expression changes in tumorigenic and wild-type mouse mammary glands identified <i>Hoxa1</i> as a possible modulator of early tumor progression. In 3D cell culture, siRNA knockdown of <i>Hoxa1</i> caused mammary epithelial tumor cells to adopt wild-type tissue architectures. In a mouse model of human breast cancer, intraductal delivery of lipid nanoparticle–formulated siRNA targeting <i>Hoxa1</i> decreased cell proliferation and tumor incidence compared with nonspecific siRNA. Next steps include profiling <i>Hoxa1</i> mutations in human breast cancer and building related computational models based on human clinical samples.</p> <p><b>SciBX 7(4); doi:10.1038/scibx.2014.113</b> Published online Jan. 30, 2014</p>	Gene regulatory network algorithm and lipid nanoparticle formulation patented; licensing status undisclosed	<p>Brock, A. <i>et al. Sci. Transl. Med.</i>; published online Jan. 1, 2014; doi:10.1126/scitranslmed.3007048  <b>Contact:</b> Donald E. Ingber, Wyss Institute for Biologically Inspired Engineering at Harvard University, Cambridge, Mass.  e-mail: <a href="mailto:don.ingber@wyss.harvard.edu">don.ingber@wyss.harvard.edu</a></p>
Breast cancer; colon cancer	Programmed cell death 1 ligand 1 (CD274 molecule; PD-L1; B7-H1)	<p>Mouse studies suggest PD-L1 inhibitors could enhance the effectiveness of radiotherapy to treat breast, colon and other cancers. In mice bearing mammary tumors, radiotherapy increased levels of Pd-11 on tumor cells and tumor-infiltrating immune cells compared with no treatment. In mice bearing mammary or colon tumors, radiotherapy and an anti-Pd-11 antibody decreased tumor growth compared with either therapy alone. Ongoing work includes investigating whether radiotherapy upregulates PD-L1 in other tumor types. Roche and its Genentech Inc. unit have RG7446 (MPDL3280A), a human mAb against PD-L1, in Phase II testing to treat non–small cell lung cancer (NSCLC) and Phase I trials to treat melanoma and other solid tumors. AstraZeneca plc has MEDI4726, a human IgG1 mAb targeting PD-L1, in Phase I testing for NSCLC, melanoma, colorectal cancer, rectal cancer and other solid tumors. Bristol-Myers Squibb Co. has BMS-936559 (MDX-1105), a human mAb against PD-L1, in Phase I trials to treat solid tumors. At least six companies have antibodies against programmed cell death 1 (PDCD1; PD-1; CD279) in Phase III or earlier development to treat cancer.</p> <p><b>SciBX 7(4); doi:10.1038/scibx.2014.114</b> Published online Jan. 30, 2014</p>	Unpatented; unlicensed; available for partnering	<p>Deng, L. <i>et al. J. Clin. Invest.</i>; published online Jan. 2, 2014; doi:10.1172/JCI67313  <b>Contact:</b> Yang-Xin Fu, The University of Chicago, Chicago, Ill.  e-mail: <a href="mailto:yfu@midway.uchicago.edu">yfu@midway.uchicago.edu</a>  <b>Contact:</b> Ralph R. Weichselbaum, same affiliation as above  e-mail: <a href="mailto:rrw@radonc.uchicago.edu">rrw@radonc.uchicago.edu</a></p>

## This week in therapeutics (continued)

Indication	Target/marker/pathway	Summary	Licensing status	Publication and contact information
Chronic lymphocytic leukemia (CLL)	Receptor tyrosine kinase-like orphan receptor 1 (ROR1)	<p>Mouse studies suggest inhibiting ROR1 could help treat CLL. In transgenic mice expressing human <i>ROR1</i> and <i>T cell leukemia/lymphoma 1A (TCL1A)</i> in B cells, CLL-like disease developed earlier than that in transgenic mice expressing either human gene alone. In <i>ROR1</i> transgenic mice engrafted with leukemia cells expressing ROR1 alone or in combination with TCL1A, an antibody targeting human ROR1 decreased leukemic cell engraftment compared with IgG control. Ongoing studies include developing a humanized antibody targeting ROR1. Kancera AB has a ROR1 inhibitor in discovery to treat CLL.</p> <p><b>SciBX 7(4); doi:10.1038/scibx.2014.115</b> Published online Jan. 30, 2014</p>	Patent application filed; available for licensing	<p>Widhopf II, G.F. <i>et al. Proc. Natl. Acad. Sci. USA</i>; published online Dec. 30, 2013; doi:10.1073/pnas.1308374111 <b>Contact:</b> Thomas J. Kipps, University of California, San Diego, La Jolla, Calif. e-mail: <a href="mailto:tkipps@ucsd.edu">tkipps@ucsd.edu</a></p>
<b>Endocrine/metabolic disease</b>				
Diabetes	Carboxylesterase 1 (CES1; hCE1)	<p><i>In vitro</i> and mouse studies suggest inhibiting CES1 could help treat type 2 diabetes. In mouse adipocytes, phenotypic screening for compounds that increased lipid storage coupled with activity-based protein profiling to indicate enzymatic targets blocked by the hits identified <i>Ces3</i>, the mouse ortholog of CES1, as the molecular target of bioactive compounds. In mouse models of diabetes, a <i>Ces3</i> inhibitor protected animals from weight gain, decreased liver lipid accumulation and increased insulin sensitivity compared with vehicle. In adipose tissue from patients with type 2 diabetes, CES1 activity was upregulated compared with that in lean controls. Next steps could include developing inhibitors of the human target.</p> <p><b>SciBX 7(4); doi:10.1038/scibx.2014.116</b> Published online Jan. 30, 2014</p>	Patent and licensing status unavailable	<p>Dominguez, E. <i>et al. Nat. Chem. Biol.</i>; published online Dec. 22, 2013; doi:10.1038/nchembio.1429 <b>Contact:</b> Enrique Saez, The Scripps Research Institute, La Jolla, Calif. e-mail: <a href="mailto:esaesz@scripps.edu">esaesz@scripps.edu</a> <b>Contact:</b> Benjamin F. Cravatt, same affiliation as above e-mail: <a href="mailto:cravatt@scripps.edu">cravatt@scripps.edu</a></p>
<b>Infectious disease</b>				
Influenza virus	Influenza A virus hemagglutinin (HA)	<p><i>In vitro</i> and mouse studies suggest CR8043 could be used as a broadly neutralizing mAb-based immunotherapy for influenza. CR8043 was produced by memory B cells obtained from donors vaccinated with seasonal influenza vaccine. In mice, CR8043 protected against H3N2 and H7N2 virus-induced death. In <i>in vitro</i> binding and trypsin cleavage studies, the mAb bound to a conserved epitope on the HA stem, inhibited conformational changes required for membrane fusion and prevented cleavage of HA that is required for infection. Next steps could include using the structure of CR8043 to guide design of a protein scaffold for vaccine studies. Johnson &amp; Johnson's Crucell N.V. unit collaborated on this study and also has the HA-targeting, broadly neutralizing antibody CR6261 in Phase I trials to treat influenza.</p> <p><b>SciBX 7(4); doi:10.1038/scibx.2014.117</b> Published online Jan. 30, 2014</p>	Patent and licensing status undisclosed	<p>Friesen, R.H.E. <i>et al. Proc. Natl. Acad. Sci. USA</i>; published online Dec. 11, 2013; doi:10.1073/pnas.1319058110 <b>Contact:</b> Ian A. Wilson, The Scripps Research Institute, La Jolla, Calif. e-mail: <a href="mailto:wilson@scripps.edu">wilson@scripps.edu</a> <b>Contact:</b> Jaap Goudsmit, Johnson &amp; Johnson Crucell Vaccine Institute, Leiden, the Netherlands e-mail: <a href="mailto:j.goudsmit@crucell.com">j.goudsmit@crucell.com</a></p>

## This week in therapeutics (continued)

Indication	Target/marker/pathway	Summary	Licensing status	Publication and contact information
Malaria	Interferon $\alpha/\beta$ receptor 1 (IFNAR1)	<p>Mouse studies suggest stimulating a type I interferon response could help improve efficacy of malaria vaccination or treatment. In mice, infection with <i>Plasmodium berghei</i> stimulated transcription of genes in the liver associated with the type I interferon response. In the <i>P. berghei</i>-infected mice, hepatocyte-specific knockout of <i>Ifnar1</i> increased parasitic liver load compared with no knockout and accelerated transition to blood-stage infection. In mice, stimulation of the type I interferon response with HCV RNA prior to <i>P. berghei</i> infection decreased parasite load compared with no stimulation. Next steps include determining the effect of type I interferon on long-term protection after malaria vaccination.</p> <p><b>SciBX 7(4); doi:10.1038/scibx.2014.118</b> Published online Jan. 30, 2014</p>	Findings unpatented; unavailable for licensing	<p>Liehl, P. <i>et al. Nat. Med.</i>; published online Dec. 22, 2013; doi:10.1038/nm.3424 <b>Contact:</b> Maria M. Mota, University of Lisbon, Lisbon, Portugal e-mail: <a href="mailto:mmota@fm.ul.pt">mmota@fm.ul.pt</a></p>
<b>Inflammation</b>				
Asthma	IL-1 $\beta$ ; IL-1 receptor; IL-17A	<p>Mouse studies suggest inhibiting IL-1<math>\beta</math> signaling could help treat obesity-associated asthma. In obese mice, levels of IL-1<math>\beta</math>-expressing macrophages in adipose tissue and the lungs were greater than those in nonobese animals. IL-1<math>\beta</math>-expressing macrophages increased airway hyperreactivity and numbers of IL-17a-producing cells in the lungs. Also in the obese mice, an IL-1 receptor antagonist decreased airway hyperreactivity and numbers of IL-17a-producing cells in the lungs compared with no treatment. Future studies could include testing anti-IL-1<math>\beta</math> antibodies in obese mice. Swedish Orphan Biovitrum AB markets Kineret anakinra, an IL-1 receptor antagonist, to treat rheumatoid arthritis (RA) and cryopyrin-associated periodic syndrome (CAPS). Bristol-Myers Squibb Co. and Novartis AG market Ilaris canakinumab (ACZ885), a human anti-IL-1<math>\beta</math> mAb, to treat CAPS. Bristol-Myers also markets the mAb to treat hyperuricemia and gout. These companies and several others have compounds targeting IL-1 receptor, IL-1<math>\beta</math> and IL-17A in Phase III and earlier testing for multiple indications including asthma.</p> <p><b>SciBX 7(4); doi:10.1038/scibx.2014.119</b> Published online Jan. 30, 2014</p>	Patent and licensing status unavailable	<p>Kim, H.Y. <i>et al. Nat. Med.</i>; published online Dec. 15, 2013; doi:10.1038/nm.3423 <b>Contact:</b> Dale T. Umetsu, Harvard Medical School, Boston, Mass. e-mail: <a href="mailto:umetsud@gene.com">umetsud@gene.com</a></p>
<b>Musculoskeletal disease</b>				
Musculoskeletal disease	Cytoglobin (CYGB)	<p><i>In vitro</i> and mouse studies suggest increasing CYGB expression could help treat muscle injury. In mouse myoblasts, siRNA against <i>Cygb</i> increased reactive oxygen species levels and apoptotic cell death compared with siRNA control, whereas overexpression of <i>Cygb</i> decreased both. In mice, skeletal muscle-specific <i>Cygb</i> knockout impaired postinjury regeneration of muscle and differentiation and proliferation of myogenic progenitor cells. Next steps include additional studies to determine the mechanism of CYGB activity.</p> <p><b>SciBX 7(4); doi:10.1038/scibx.2014.120</b> Published online Jan. 30, 2014</p>	Patent application filing in progress; licensing status not applicable	<p>Singh, S. <i>et al. Proc. Natl. Acad. Sci. USA</i>; published online Dec. 23, 2013; doi:10.1073/pnas.1314962111 <b>Contact:</b> Pradeep P.A. Mammen, The University of Texas Southwestern Medical Center, Dallas, Texas e-mail: <a href="mailto:pradeep.mammen@utsouthwestern.edu">pradeep.mammen@utsouthwestern.edu</a> <b>Contact:</b> Beverly A. Rothermel, same affiliation as above e-mail: <a href="mailto:beverly.rothermel@utsouthwestern.edu">beverly.rothermel@utsouthwestern.edu</a></p>

## This week in therapeutics (continued)

Indication	Target/marker/ pathway	Summary	Licensing status	Publication and contact information
<b>Neurology</b>				
Alzheimer's disease (AD)	Phospholipase D3 (PLD3)	Human sample and <i>in vitro</i> studies suggest stimulating PLD3 activity could help treat a subset of patients with late-onset AD. In 29 samples from 14 different families with late-onset AD, sequence analysis identified rare variants in <i>PLD3</i> that correlated with increased risk for late-onset AD. In human brain samples, <i>PLD3</i> expression was lower in samples from patients with AD than in those from healthy individuals. In a mouse neuroblastoma cell line, overexpression of <i>PLD3</i> decreased accumulation of extracellular pathogenic $\beta$ -amyloid ( $A\beta$ ) proteins, whereas shRNA knockdown of <i>PLD3</i> increased accumulation. Next steps include examining the effects of mutant and wild-type <i>PLD3</i> levels on $A\beta$ levels in cell and animal models.  <b>SciBX 7(4); doi:10.1038/scibx.2014.121 Published online Jan. 30, 2014</b>	Patent status undisclosed; available for licensing through Washington University in St. Louis	Cruchaga, C. <i>et al. Nature</i> ; published online Dec. 11, 2013; doi:10.1038/nature12825 <b>Contact:</b> Carlos Cruchaga, Washington University in St. Louis, St. Louis, Mo. e-mail: <a href="mailto:ccruchaga@wustl.edu">ccruchaga@wustl.edu</a>
Post-traumatic stress disorder (PTSD)	Histone deacetylase 2 (HDAC2)	Mouse studies suggest HDAC2 inhibitors could help treat PTSD associated with long-term traumatic memories. In mice receiving a fear-extinction treatment protocol 1 day after fear conditioning, compared with mouse models receiving the protocol after 30 days, conditioned fear responses decreased and Hdac2-chromatin dissociation in hippocampal neurons increased. In mice receiving the protocol 30 days after conditioning, a class I HDAC inhibitor decreased conditioned fear responses and increased synaptic and structural plasticity of hippocampal neurons compared with vehicle. Future studies could include developing and testing HDAC2-specific inhibitors in the mouse models. Acetylon Pharmaceuticals Inc. has ACY-738, a selective inhibitor of HDAC1 and HDAC2, in preclinical testing to treat neurological indications. Acetylon also has a selective HDAC1 and HDAC2 inhibitor in preclinical testing to treat sickle cell disease and thalassemia ( <i>see PTSD: rewriting fearful memories, page 9</i> ).  <b>SciBX 7(4); doi:10.1038/scibx.2014.122 Published online Jan. 30, 2014</b>	Patent and licensing status unavailable	Gräff, J. <i>et al. Cell</i> ; published online Jan. 16, 2014; doi:10.1016/j.cell.2013.12.020 <b>Contact:</b> Li-Huei Tsai, Massachusetts Institute of Technology, Cambridge, Mass. e-mail: <a href="mailto:lhtsai@mit.edu">lhtsai@mit.edu</a>

## This week in therapeutics (continued)

Indication	Target/marker/ pathway	Summary	Licensing status	Publication and contact information
<b>Renal disease</b>				
Renal disease	Angiotensin-like 4 (ANGPTL4); integrin $\alpha_v\beta_3$	Rat studies suggest ANGPTL4 variants that selectively bind to integrin $\alpha_v\beta_3$ could help prevent proteinuria in nephrotic syndrome. Proteinuria and hypertriglyceridemia are hallmarks of nephrotic syndrome but have not been functionally linked. In rat models of a precursor phase of nephrotic syndrome, <i>Angptl4</i> overexpression in adipose tissue increased plasma levels of Angptl4, which decreased proteinuria but also increased hypertriglyceridemia, compared with normal <i>Angptl4</i> expression. In the same models, a recombinant, mutant form of ANGPTL4 that did not interact with lipoprotein lipase (Lpl) but retained its interaction with $\alpha_v\beta_3$ on renal cells decreased proteinuria compared with wild-type ANGPTL4 without raising triglyceride levels. Ongoing studies include pharmacokinetic studies of ANGPTL4 mutants and scaling up production of the proteins for preclinical toxicity studies.  <b>SciBX 7(4); doi:10.1038/scibx.2014.123</b> <b>Published online Jan. 30, 2014</b>	Patent application filed covering use of ANGPTL4 mutants in proteinuric disorders; available for licensing from the UAB Research Foundation <b>Contact:</b> Deborah J. Bidanset-Ponder, UAB Research Foundation, Birmingham, Ala. e-mail: <a href="mailto:debbie@uab.edu">debbie@uab.edu</a>	Clement, L.C. <i>et al. Nat. Med.</i> ; published online Dec. 8, 2013; doi:10.1038/nm.3396 <b>Contact:</b> Sumant S. Chugh, The University of Alabama at Birmingham, Birmingham, Ala. e-mail: <a href="mailto:chugh@uab.edu">chugh@uab.edu</a>
<b>Various</b>				
Allergy; allergic rhinitis; atopic dermatitis	S100 calcium binding protein A4 (S100A4)	Human and mouse studies suggest inhibiting S100A4 could help treat allergy. In patients with allergic rhinitis or allergic dermatitis, S100A4 levels in nasal fluid or skin lesions were higher than those in corresponding samples from healthy controls. In blood monocytes from the patients with rhinitis, an anti-S100A4 antibody decreased levels of allergy-associated, proinflammatory cytokines compared with pretreatment baselines. In mouse models of atopic dermatitis, the anti-S100A4 antibody decreased skin inflammation, leukocyte recruitment to the skin and draining lymph nodes, and circulating levels of T helper type 2 (Th2) cell IgG compared with an inactive antibody. Ongoing work includes investigating the role of S100A4 in asthma.  Lykera Biomed S.A. has LK-1, a humanized antibody against S100A4, in preclinical development to treat pancreatic cancer.  <b>SciBX 7(4); doi:10.1038/scibx.2014.124</b> <b>Published online Jan. 30, 2014</b>	Unpatented; available for licensing	Bruhn, S. <i>et al. Sci. Transl. Med.</i> ; published online Jan. 8, 2014; doi:10.1126/scitranslmed.3007410 <b>Contact:</b> Mikael Benson, Linköping University, Linköping, Sweden e-mail: <a href="mailto:mikael.benson@liu.se">mikael.benson@liu.se</a> <b>Contact:</b> Zou Xiang, University of Gothenburg, Gothenburg, Sweden e-mail: <a href="mailto:zou.xiang@gu.se">zou.xiang@gu.se</a>

## 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>Assays &amp; screens</b>			
Humanized mice to select for improved recombinant adeno-associated vectors (AAVs) for gene therapy	Humanized mice could help screen for and select clinically relevant AAVs for gene therapy. The transduction efficiency of recombinant AAVs in animal models often does not translate to humans. Chimeric mice with humanized livers were used to select for AAVs capable of efficient cellular uptake, internalization and replication. In the mice, delivery of a fluorescent reporter gene using one of the most effective AAVs transfected about 43% of human hepatocytes, whereas AAV8, a clinically tested, liver-specific vector, transfected about 4% of cells. Next steps could include using additional humanized mouse models to identify AAVs selective for other human tissues.  <b>SciBX 7(4); doi:10.1038/scibx.2014.125</b> <b>Published online Jan. 30, 2014</b>	Patent application filed; available for licensing	Lisowski, L. <i>et al. Nature</i> ; published online Dec. 25, 2013; doi:10.1038/nature12875 <b>Contact:</b> Mark A. Kay, Stanford University School of Medicine, Stanford, Calif. e-mail: <a href="mailto:markay@stanford.edu">markay@stanford.edu</a>
<b>Chemistry</b>			
Nontoxic and biocompatible hydrophobic light-activated adhesive (HLAA) as a hemostatic seal	A nontoxic and biocompatible HLAA could help reconnect tissue in the presence of blood during reconstructive cardiovascular surgery. A prepolymer was mixed with a photoinitiator composed of UV cross-linkable HLAA to form a flexible film. In rat hearts, poly(glycerol sebacate urethane) patches coated with HLAA under wet conditions attached to the epicardial surface and remained attached after seven days. In multiple animal models, HLAA-coated patches were used to close defects in the left ventricle wall of 17 of 19 rats, in the ventricular septum of 4 of 4 pigs and in the carotid arteries of 4 of 4 pigs. Next steps include safety and efficacy evaluations of vascular reconstruction in large animals.  <b>SciBX 7(4); doi:10.1038/scibx.2014.126</b> <b>Published online Jan. 30, 2014</b>	Patented; licensed to Gecko Biomedical S.A.S.	Lang, N. <i>et al. Sci. Transl. Med.</i> ; published online Jan. 8, 2014; doi:10.1126/scitranslmed.3006557 <b>Contact:</b> Pedro J. del Nido, Boston Children's Hospital, Boston, Mass. e-mail: <a href="mailto:pedro.delnido@cardio.chboston.org">pedro.delnido@cardio.chboston.org</a> <b>Contact:</b> Jeffrey M. Karp, Brigham and Women's Hospital, Cambridge, Mass. e-mail: <a href="mailto:jmkarp@partners.org">jmkarp@partners.org</a>
<b>Disease models</b>			
High-fidelity prostate cancer xenograft models from fresh patient prostate cancer samples	A collection of xenograft mice created using fresh patient prostate cancer tissue samples could help identify new therapeutics for the disease. In immunocompromised mice, serial subrenal transplantation of primary or metastatic prostate cancer samples taken from patients after initial surgery or needle biopsy established 12 transplantable tumor lines, including 2 lines from metastatic neuroendocrine prostate cancers. Tumors in the xenograft models maintained the histopathological, genetic and molecular characteristics of the patient tumors and had similar tumor growth patterns and outcomes as the matched patients. Next steps could include using the models to identify new therapeutics.  <b>SciBX 7(4); doi:10.1038/scibx.2014.127</b> <b>Published online Jan. 30, 2014</b>	Patent and licensing status unavailable	Lin, D. <i>et al. Cancer Res.</i> ; published online Dec. 19, 2013; doi:10.1158/0008-5472.CAN-13-2921-T <b>Contact:</b> Yuzhuo Wang, BC Cancer Agency, Vancouver, British Columbia, Canada e-mail: <a href="mailto:ywang@bccrc.ca">ywang@bccrc.ca</a>
Mouse model of traumatic brain injury (TBI)	A mouse model of TBI could be useful for studying inflammatory mechanisms in the disease and screening for potential treatments. To mimic TBI, mice underwent surgical thinning and compression of the skull. Transcranial imaging of the injury site revealed proinflammatory innate immune activity and apoptosis. Local administration of purinergic receptor antagonists showed that acute inflammation protects against cell death. Next steps include identifying and testing drug candidates that modulate inflammatory response and cell death in the model.  <b>SciBX 7(4); doi:10.1038/scibx.2014.128</b> <b>Published online Jan. 30, 2014</b>	Patent and licensing status undisclosed	Roth, T.L. <i>et al. Nature</i> ; published online Dec. 8, 2013; doi:10.1038/nature12808 <b>Contact:</b> Dorian B. McGavern, National Institutes of Health, Bethesda, Md. e-mail: <a href="mailto:mcgavern@mail.nih.gov">mcgavern@mail.nih.gov</a>

## This week in techniques (continued)

Approach	Summary	Licensing status	Publication and contact information
<b>Drug platforms</b>			
Monovalent, transferrin receptor-binding antibody with improved blood brain barrier (BBB) penetration	A monovalent, transferrin receptor-binding Fab fragment could be used to improve the delivery of antibodies through the BBB. An antibody was constructed that consisted of a single transferrin receptor-binding Fab fragment fused to the C-terminal end of the heavy chain of a $\beta$ -amyloid (A $\beta$ )-specific mAb. In a mouse model of amyloid precursor protein (APP)-driven amyloidosis, the engineered antibody improved parenchymal exposure and increased A $\beta$ binding in the brain by 50-fold compared with an unmodified A $\beta$ mAb. In a mouse model of Alzheimer's disease (AD), the engineered antibody decreased A $\beta$ plaque burden more efficiently than the unmodified A $\beta$ mAb. Next steps include generating modular, monovalent, transferrin receptor-binding antibodies specific to primate and human receptors (see <b>BBB-conquering antibodies</b> , page 1).	Patent and licensing status undisclosed	Niewoehner, J. <i>et al. Neuron</i> ; published online Jan. 8, 2014; doi:10.1016/j.neuron.2013.10.061 <b>Contact:</b> Per-Ola Freskgård, Roche, Basel, Switzerland e-mail: <a href="mailto:per-ola.freskgard@roche.com">per-ola.freskgard@roche.com</a> <b>Contact:</b> Anirvan Ghosh, same affiliation as above e-mail: <a href="mailto:anirvan.ghosh@roche.com">anirvan.ghosh@roche.com</a>
	<b>SciBX 7(4); doi:10.1038/scibx.2014.129</b> Published online Jan. 30, 2014		
Simian immunodeficiency virus (SIV) and HIV env variants conferring vaccine escape	Determining amino acid variations in HIV strains that escape neutralizing antibodies could help guide vaccine design. In rhesus macaques immunized with DNA encoding SIV <sub>Mac239</sub> env, DNA sequencing of viruses that bypassed the protective effect of the vaccine revealed common single amino acid variations that conferred resistance to immunization-elicited antibodies. In a collection of 51 HIV-1 viruses, a fraction of neutralization-resistant viruses exhibited amino acid variation corresponding to that seen in neutralization-resistant SIV strains, suggesting a conserved escape mechanism. Next steps could include analyzing HIV sequences from HIV vaccine trials to determine additional vaccine-specific repertoires of resistance-conferring mutations and using the data to design new vaccines.	Patent and licensing information undisclosed	Roederer, M. <i>et al. Nature</i> ; published online Dec. 18, 2013; doi:10.1038/nature12893 <b>Contact:</b> Mario Roederer, National Institutes of Health, Bethesda, Md. e-mail: <a href="mailto:roederer@nih.gov">roederer@nih.gov</a>
	<b>SciBX 7(4); doi:10.1038/scibx.2014.130</b> Published online Jan. 30, 2014		
<b>Markers</b>			
Fc $\gamma$ -receptor IIc (CD32C; FCGR2C) variants predict responses to vaccines	Human studies suggest expression of CD32C could help predict patient responses to vaccines. CD32C normally contains a termination codon, but 7%–15% of individuals carry a mutation that changes it into a full-length open reading frame. Individuals with this variant expressed CD32C on B cells and were more likely to respond to an anthrax vaccine than patients that did not express the variant. Individuals with the full-length CD32C variant also were more likely to develop the autoimmune disease systemic lupus erythematosus (SLE) than those without the variant. Next steps could include validating the association of the variant with immune responses in additional individuals.	Patent and licensing status unavailable	Li, X. <i>et al. Sci. Transl. Med.</i> ; published online Dec. 18, 2013; doi:10.1126/scitranslmed.3007097 <b>Contact:</b> Robert P. Kimberly, The University of Alabama at Birmingham, Ala. e-mail: <a href="mailto:rpk@uab.edu">rpk@uab.edu</a> <b>Contact:</b> Jeffrey C. Edberg, same affiliation as above e-mail: <a href="mailto:jedberg@uab.edu">jedberg@uab.edu</a>
	<b>SciBX 7(4); doi:10.1038/scibx.2014.131</b> Published online Jan. 30, 2014		
Forkhead box P3 (FOXP3)-depleted T helper type 17 (Th17) cells as an arthritis biomarker	Mouse studies suggest T <sub>reg</sub> cells that lose expression of FOXP3 and become Th17 cells can contribute to arthritis and could provide a useful biomarker to aid arthritis drug development. In a mouse model of collagen-induced arthritis, a population of Foxp3 <sup>+</sup> T cells lost Foxp3 expression, converted into Th17 cells and led to joint swelling and bone destruction. In cell culture, the conversion into Th17 cells depended on the presence of synovial fibroblasts and the production of Il-6. Next steps include identifying a molecular signature specific to Foxp3-depleted T cells that could serve as a biomarker or reveal potential therapeutic targets.	Unpatented; licensing status not applicable	Komatsu, N. <i>et al. Nat. Med.</i> ; published online Dec. 22, 2013; doi:10.1038/nm.3432 <b>Contact:</b> Hiroshi Takayanagi, The University of Tokyo, Tokyo, Japan e-mail: <a href="mailto:takayana@m.u-tokyo.ac.jp">takayana@m.u-tokyo.ac.jp</a>
	<b>SciBX 7(4); doi:10.1038/scibx.2014.132</b> Published online Jan. 30, 2014		

**Erratum: The Distillery: cancer: lymphoma**

SciBX 7(3); doi:10.1038/scibx.2014.84

Published online Jan. 23, 2014

A Therapeutics item on cancer, highlighting an article by Kohrt *et al.*, misstated the target. The target/marker/pathway column should read “Killer cell immunoglobulin-like receptor three domains long cytoplasmic tail 1 (KIR3DL1; CD158E1); KIR3DL2 (CD158K); KIR3DL3 (CD158Z); CD20.” All instances of the targets in the summary should read “KIR3DL” or “CD20.”

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Cytoglobin	15	Il-17	11	PLD3	16		
		IL-17A	15				
		IL-1 $\beta$	15				
		Il-6	19				

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