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By Benjamin Boettner, Associate Editor

Conflicting results from two 2012 studies made it unclear whether IL-18 was a cause of or a potential therapy for age-related macular degeneration.<sup>1,2</sup> A tiebreaker study suggests the latter, showing that the cytokine was at least as effective as a VEGF inhibitor in mouse models of wet age-related macular degeneration.<sup>3</sup>

Age-related macular degeneration (AMD) is the leading cause of blindness in people older than 65 and affects 30–50 million people worldwide. In about 10% of patients, the disease progresses to the wet form, which is characterized by choroidal neovascularization (CNV)—newly sprouting blood vessels originating from the outer vascular layer of the eye.

These vessels break through the retinal pigment epithelium (RPE), where they hemorrhage. The resulting blood clots damage the RPE, leaving photoreceptors unprotected and causing them to degenerate.<sup>4</sup> Wet AMD typically is treated with intravitreal injections of molecules that inhibit VEGF.

In 2012, a team at **Trinity College Dublin** led by Matthew Campbell and Sarah Doyle found a new target in the disease. The team reported a protective role for the Nlr family pyrin domain containing 3 (Nlrp3; Nalp3; Cias1) inflammasome and its downstream effector IL-18.<sup>1</sup>

Campbell is a research assistant professor at the **Smurfit Institute of Genetics at Trinity College Dublin**. Doyle is an assistant professor at the **Trinity College Dublin School of Medicine**.

That same year, however, researchers at the **University of Kentucky** reported that intravitreal injection of recombinant human IL-18 provoked an AMD phenotype in mice.<sup>2</sup>

The newest study from Campbell and Doyle supports their original findings.<sup>3</sup>

In a mouse model of wet AMD, the group intravitreally injected recombinant human IL-18 alone or in combination with a murine Vegf-neutralizing antibody. IL-18 by itself reduced the severity of CNV at least as efficiently as the anti-VEGF antibody. The combination showed additive effects.

Moreover, the researchers showed that systemically increasing levels of IL-18 also protected mice against CNV. Systemic IL-18 treatment for two weeks before induction of CNV suppressed neovascularization and boosted the effects of the intravitreally injected anti-Vegf antibody. The team did not directly compare systemic IL-18 with intravitreal anti-Vegf therapy.

Results were published in *Science Translational Medicine*. The study was coauthored by researchers from the **Royal Victoria Eye and Ear Hospital**, the **National Eye Institute** of the NIH and the Ophthalmic Discovery Performance Unit of **GlaxoSmithKline plc**, which provided the recombinant human IL-18.

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PO Box 1246  
San Carlos, CA 94070-1246  
T: +1 650 595 5333Chicago  
20 N. Wacker Drive, Suite 1465  
Chicago, IL 60606-2902  
T: +1 312 755 0798United 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

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“The paper describes a somewhat counterintuitive approach for the treatment of CNV secondary to wet AMD—using a proinflammatory cytokine, namely IL-18, to dampen later stage VEGF-mediated choroidal vessel angiogenesis,” said Kay Rittenhouse, senior director of ophthalmology and external R&D innovation at **Pfizer Inc.**

Mechanistically, Campbell thinks that “it is highly likely that IL-18 is acting directly on endothelial cells when injected intravitreally. However, when administered systemically, IL-18 is likely inducing specific subpopulations of immune cells—NK cells and activated T cells—that have antiangiogenic potency.” Studies to determine the actual mechanism are under way in Campbell’s laboratory.

According to Rittenhouse, it will be important to determine “whether the mechanism by which IL-18 dampens neovascularization is due to its proinflammatory activity.”

**Envisioning the IL-18 path**

According to Rittenhouse and Campbell, the contradictory results from the Trinity team and the University of Kentucky group could be explained by the different doses of IL-18 used in the studies.

The exact IL-18 concentrations were not specified in the 2012 report by the Kentucky team. Based on titration curves performed by the Trinity team, Campbell said that the other group almost certainly used doses of IL-18 that were above a therapeutic and physiological threshold and could have damaged the RPE.

Doyle noted that the Trinity team also saw adverse effects on the RPE and other retinal cells at extremely high doses of IL-18.

Alternatively, Rittenhouse told SciBX that “recombinant IL-18s may differ structurally from one another in important ways that link

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to responses. These structural characteristics need to be highlighted to minimize potential adverse effects.”

With the strengthened case for using IL-18 to treat AMD, Lois Smith, a professor of ophthalmology at **Harvard Medical School** and the **Boston Children’s Hospital**, thinks that the next step should be the clinic.

She said that animal models of AMD have multiple shortcomings and noted that inflammatory and gene expression changes in response to burns or injury as occurs in laser-induced CNV differ markedly between mice and humans.<sup>5</sup>

“It could be possible to test IL-18 in a small pilot study in human subjects with advanced AMD that already have lost vision but whose retinas still allow observations of effects on the neovasculature,” said Smith.

Campbell said that Trinity College and its clinical partners are designing a trial of IL-18 in patients with wet AMD.

“Although IL-18 alone appears to contain CNV as

well as anti-VEGF treatment, it is likely that, to begin with, a combined therapy might be most acceptable,” said Doyle. She added that the Trinity team is conducting preclinical studies to further define the safety and mechanism of action of IL-18 treatment.

Trinity has filed for a patent covering the use of recombinant human IL-18 to treat CNV secondary to wet AMD. GlaxoSmithKline has an option to license the IP.

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**Contact:** Matthew Campbell, Smurfit Institute of Genetics at Trinity College Dublin, Dublin, Ireland  
e-mail: [matthew.campbell@tcd.ie](mailto:matthew.campbell@tcd.ie)
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#### COMPANIES AND INSTITUTIONS MENTIONED

**Boston Children’s Hospital**, Boston, Mass.  
**GlaxoSmithKline plc** (LSE:GSK; NYSE:GSK), London, U.K.  
**Harvard Medical School**, Boston, Mass.  
**National Eye Institute**, Bethesda, Md.  
**National Institutes of Health**, Bethesda, Md.  
**Pfizer Inc.** (NYSE:PFE), New York, N.Y.  
**Royal Victoria Eye and Ear Hospital**, Dublin, Ireland  
**Smurfit Institute of Genetics at Trinity College Dublin**, Dublin, Ireland  
**Trinity College Dublin**, Dublin, Ireland  
**Trinity College Dublin School of Medicine**, Dublin, Ireland  
**University of Kentucky**, Lexington, Ky.

**“It could be possible to test IL-18 in a small pilot study in human subjects with advanced AMD that already have lost vision but whose retinas still allow observations of effects on the neovasculature.”**

—Lois Smith, Harvard Medical School

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# Scripps looks outward

By Chris Cain, Senior Writer

The Scripps Research Institute has borrowed a page from the VC playbook and formed a separate corporation called **Scripps Advance LLC** that will house assets and IP related to discrete early stage research projects. The goal is to attract pharma investment in translational assets. **Johnson & Johnson's** California Innovation Center is on board as Scripps Advance's first partner.

Two years ago Scripps decided to move away from the institute-wide option agreements it previously maintained with pharma companies including **Pfizer Inc.** and **Novartis AG**.<sup>1</sup>

At the time, Scripps said that this was because the pacts did not have clearly defined aims and were not bringing enough compounds or technologies to market.

The institute instead has focused on deals that are limited to specific therapeutic areas. In 2013 Scripps partnered with **Takeda Pharmaceutical Co. Ltd.** to identify new compounds for neurological and psychological diseases and with the Janssen unit of J&J and the **Crucell Vaccine Institute** on infectious disease projects.

Scripps Research Institute VP of business development Scott Forrest told *SciBX* that in lieu of another big partnership, “a better way to do this has been to have more focused deals that are strategically aligned between both parties. These partnerships have been thematically consistent in that we jointly negotiate a work plan before they are even started.”

Forrest said that the next step was to identify specific research projects that could be attractive to pharma. To facilitate this, Scripps created a separate business entity to make the investment more flexible from an accounting standpoint.

“By structuring Scripps Advance as a separate LLC that can do the sourcing and management and house the IP of a project in a subsidiary company, this allows you to switch the investment onto the balance sheet of a pharma instead of their profit and loss [statement],” said Forrest.

He pointed to Arteaus Therapeutics LLC as an example of this structure. The company was launched in 2011 by **Atlas Venture** and **OrbiMed Advisors LLC** to in-license and develop LY2951742, an antibody targeting calcitonin gene-related peptide (CGRP) from **Eli Lilly and Co.** After the compound met the primary and secondary endpoints in a Phase II trial to prevent recurring migraines, Eli Lilly reacquired the antibody.<sup>2</sup>

“VCs have been hip to this game for a little while now. Academic groups have watched it, noodled with it, but not attempted it in a robust fashion,” Forrest said.

To develop chemical matter against targets, Scripps Advance will rely on its **Scripps Florida** molecular screening center, one of four large centers that were funded by the **NIH** molecular libraries program.

Forrest said that the capabilities of the Florida center will allow it to advance projects both from within Scripps and from other institutions that do not have access to such a center.

Thorsten Melcher, senior director for new ventures and

partnerships at the J&J California Innovation Center, told *SciBX* that the pharma decided to partner with Scripps on the strength of the molecular screening center and Scripps' willingness to look outside for partners.

“Scripps Florida has chemistry and DMPK [drug metabolism and pharmacokinetics] capabilities not typically associated with an academic institution,” said Melcher.

J&J's financial contribution to Scripps Advance is undisclosed. A joint steering committee made up of representatives from Scripps and J&J will identify projects to pursue. Todd Huffman, head of new ventures at Scripps and president of Scripps Advance, said that projects will receive seed funding from Scripps Advance.

Scripps Advance hopes to partner with two to three additional pharmas.

## Lockdown

The first company launched by Scripps Advance is **Padlock Therapeutics Inc.**, which is developing inhibitors of peptidyl arginine deiminase (PADI; PAD).

The company was cofounded by Huffman; Paul Thompson, an associate professor of chemistry at Scripps Florida; and Kerri Mowen, an assistant professor of chemical physiology at Scripps Florida.

Atlas executive-in-residence and Padlock CEO Michael Gilman told *SciBX* that the company is focusing on the role of PADs in producing autoantigens in autoimmune diseases.

PADs act on arginine residues in proteins to produce citrulline, and antibodies targeting citrullinated proteins have been associated with autoimmune diseases including lupus and rheumatoid arthritis (RA).

In a 2013 article in *The Journal of Clinical Investigation*, Thompson showed that inhibiting PAD activity could improve endothelial dysfunction and reduce thrombosis risk.<sup>3</sup> In a 2014 paper in *ACS Chemical Biology*, Thompson's lab, in collaboration with the Scripps molecular screening center, described compounds that inhibit PAD by locking the enzyme in its inactive apo conformation.<sup>4</sup>

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**Atlas Venture**, Cambridge, Mass.  
**Crucell Vaccine Institute**, Leiden, the Netherlands  
**Eli Lilly and Co.** (NYSE:LLY), Indianapolis, Ind.  
**Johnson & Johnson** (NYSE:JNJ), New Brunswick, N.J.  
**National Institutes of Health**, Bethesda, Md.  
**Novartis AG** (NYSE:NVS; SIX:NOVN), Basel, Switzerland  
**OrbiMed Advisors LLC**, New York, N.Y.  
**Padlock Therapeutics Inc.**, Cambridge, Mass.  
**Pfizer Inc.** (NYSE:PFE), New York, N.Y.  
**Scripps Advance LLC**, Jupiter, Fla.  
**Scripps Florida**, Jupiter, Fla.  
**The Scripps Research Institute**, La Jolla, Calif.  
**Takeda Pharmaceutical Co. Ltd.** (Tokyo:4502), Osaka, Japan

# Stem cell disarray

By C. Simone Fishburn, Senior Editor

With its Center for Regenerative Medicine having produced only one program ready for clinical testing in the last four years, the NIH is rethinking its strategy for translating stem cell therapies. When the NIH holds a stem cell workshop next month to map out its path forward, many stakeholders hope the message will be that the NIH should focus less on drug development and more on standardizing procedures and protocols.

Clinical progress of stem cell therapies has yet to gain momentum because there are many drug development hurdles caused by the fact that this type of treatment has so many differences from other more common therapeutic modalities.

For example, unlike small molecules, which can be manufactured, characterized and purified to well-defined and uniform standards, “with autologous therapy, the patient is the source of the product, so you’re not in control of the manufacturing of the product; you’re just transplanting it,” said Douglas Losordo, CMO of stem cell company **NeoStem Inc.** “There’s no playbook for much of this right now.”

The NIH created the Center for Regenerative Medicine (NIH CRM) in part to help address those differences.

According to James Anderson, director for program coordination, planning and strategic initiatives at the NIH, the impetus for launching the center dates to 2009, when Francis Collins said that an intramural research program was needed to overcome the hurdles in stem cell research.

However, the emphasis shifted to include drug development activities, and in 2010 the NIH CRM was established by the NIH Common Fund to help drive in-house programs to the clinic.

“There was not a lot of stem cell work oriented at overcoming obstacles to cell therapy. There was lots of biology work, but it wasn’t patient oriented. NIH wanted to establish a program using its own clinical facilities, focused on getting cell therapy to patients that would ultimately help inform the field,” Anderson said.

From inception through 2013, CRM received \$16 million in funding from the NIH Common Fund.

For the first two years, the center used its pilot funds to stimulate intramural interest in working on basic stem cell biology with seminars, workshops with the FDA and meetings with biotechs. The next step, Anderson said, was for investigators to advance their programs to the clinic within a defined period of time.

Four years on, the program has not spawned the clinical programs the center had hoped for, and “only one project was ready for the launching pad,” Anderson said. “We don’t have enough different synergistic projects moving forward.”

In late March, NIH CRM director Mahendra Rao stepped down, and the institute announced it would hold workshops in May to define what it should accomplish, identify priorities and map out the time line for the next few years.

“We’re stepping back and asking the question again—where can

we have a broad impact that will help the community move forward?” Anderson asked.

## Role-play

Rao—who has joined **The New York Stem Cell Foundation** (NYSCF) as VP of regenerative medicine—told *SciBX* that the time is ripe for re-examining what roles the NIH, not-for-profit organizations, academia and industry should play in the field.

“Different people are trying to play too many roles. Some institutions are trying to do everything and are dropping the ball,” he said. According to Rao, the private sector and not-for-profit organizations are best placed to create new stem cell therapies and move them to the clinic. He said that the NIH should focus on identifying the procedural steps needed to take a product to the clinic, such as standardizing how to write patient consent forms.

Anderson agreed that the NIH’s role could include solving technical and regulatory challenges such as what cell culture matrix to use, what experimental steps are needed to get to the clinic, what protocols to use to differentiate and isolate cells, what biomarkers to use and how to

image the cells when they are reintroduced into animals or humans.

“People are thinking about one-off ‘my-lab’ experiments rather than what are the overall obstacles in the field,” he said.

Susan Solomon, cofounder and CEO of NYSCF, also thought that the NIH should rethink its role in the field. “The role of government typically is not to do breakthrough work but to scale up research done in the private and philanthropic sector,” she said.

For example, Solomon said, NYSCF could benefit from help with scaling up its program to create living bone from induced pluripotent stem (iPS) cells. In 2013, NYSCF scientists found a way to generate vascularized bone but could only produce bone that was the length of a fingertip.<sup>1</sup> To use the technology to replace craniofacial damage, a hip joint or a leg bone, the system would need considerable scaling.

A government organization could have the resources and capabilities to help reach the necessary scale, said Solomon, because companies are still cautious about investing in this field.

Jason Gardner, head of **GlaxoSmithKline plc’s** Regenerative Medicine Discovery Performance Unit, told *SciBX* that the field could benefit from a consortium model with industry and academia, driven by the NIH, similar to the Accelerated Medicines Partnership.<sup>2</sup>

Interactions with industry should come as early as possible, he said. For example, industry could advise academics on what types of data would be important and could give input to dose-response design and dosing frequency.

“These are hard trials to get right. That interface is important,” he said.

Anderson agreed that the NIH could act as a facilitator. “The unique thing that NIH can do is convene the interested parties and figure out how we can approach this together,” he said.

Gardner said that standardization of protocols and characterization of cells for safety, consistency, scalability and reproducibility are challenges that need to be addressed.

“This is a good pause point in terms of the expectations of certain groups for the translatability [of stem cell therapies],” he said.

“We’re stepping back and asking the question again—where can we have a broad impact that will help the community move forward?”

—James Anderson,  
National Institutes of Health

In addition, he said that “it would benefit the field tremendously if there were more global harmonization.” Different regulations between the U.S., Europe and the U.K. add further complexity.

Rao said that the U.S. and other countries should watch Japan, who changed its regulations about clinical trials related to stem cells to accelerate translation.

The new law, passed by the House of Councillors of Japan’s parliament in late 2013, allows products to receive conditional approval for marketing if they are shown to be safe, without requiring demonstration of efficacy in Phase II clinical trials. Full approval would be granted after comprehensive studies confirm safety and efficacy in a wider population.

“This could turn out to be very important as a fundamental change for Japanese investigators and might get emulated by other countries,” he said.

### Risk reduction

Although companies have adopted various stem cell technologies in their screening efforts, few have gone down the therapeutic path. According to Solomon, the NIH should help solve logistical problems in translating innovations to the clinic, whereas not-for-profit organizations should focus on derisking early stage research.

“Private philanthropy can do the high-risk, high-return research with no preliminary data and with no certainty that it will work,” she said. “Commercially, it doesn’t make sense to take that risk. The failure rate of new drugs is too high to add this kind of risk around the technology.”

NYSFCF has about 45 internal scientists and funds another 60 scientists in external academic labs, with a total budget of about \$22 million.

Elona Baum, general counsel and VP of business development at the **California Institute for Regenerative Medicine** (CIRM), also thinks that the risk in the field is still too high for some large pharmaceutical companies. She said that the CIRM contributes to

derisking by funding preclinical work in addition to Phase I and II proof-of-concept studies.

Baum noted that the stem cell space has seen a trickle of deal activity this year. In January, **Capricor Therapeutics Inc.** partnered with **Johnson & Johnson’s** Janssen Biotech Inc. subsidiary to develop Capricor’s cell therapy programs for cardiologic applications. The deal included lead compound CAP-1002. The allogeneic, cardiosphere-derived stem cells are in Phase I/II testing to treat myocardial infarction (MI).

Also in January, **Sangamo BioSciences Inc.** partnered with **Biogen Idec Inc.** to use Sangamo’s zinc finger nuclease technology to develop cell therapies to treat  $\beta$ -thalassemia and sickle cell disease.

Both Sangamo’s and Capricor’s projects had received funding from the CIRM prior to the partnerships.

Although those deals have not opened any floodgates, Baum said that she has had discussions with five different pharma R&D heads and expects to see another one or two stem cell deals this year.

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2. Fishburn, C.S. *SciBX* 7(8); doi:10.1038/scibx.2014.215

### COMPANIES AND INSTITUTIONS

- Biogen Idec Inc.** (NASDAQ:BIIB), Weston, Mass.
- California Institute for Regenerative Medicine**, San Francisco, Calif.
- Capricor Therapeutics Inc.** (OTCQB:CAPR), Beverly Hills, Calif.
- GlaxoSmithKline plc** (LSE:GSK; NYSE:GSK), London, U.K.
- Johnson & Johnson** (NYSE:JNJ), New Brunswick, N.J.
- National Institutes of Health**, Bethesda, Md.
- NeoStem Inc.** (NASDAQ:NBS), New York, N.Y.
- The New York Stem Cell Foundation**, New York, N.Y.
- Sangamo BioSciences Inc.** (NASDAQ:SGMO), Richmond, Calif.

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# Superhuman mice

By Tracey Baas, Senior Editor

The paradox of current mouse-based antibody platforms is that the Ig gene manipulations used to generate the mice can limit the animals' ability to produce robust antibody responses. **Kymab Ltd.** and **Regeneron Pharmaceuticals Inc.** have now published details about how their newest mouse platforms circumvent these issues and improve antibody diversity and affinity.<sup>1-3</sup>

Past approaches to engineering mice to develop human antibodies relied on the sequential random insertion of human Ig genes and partial or total elimination of the equivalent mouse Ig genes.

As a result of these gene manipulations, animals lacked fully functional immune systems, which limited their ability to produce responses to some antigens.<sup>4-6</sup> In addition, sequence replacement was limited to about 100 kb, and the transformation process required up to four rounds of embryonic stem-cell manipulations.<sup>7</sup>

Hampered immune system function was thought to be due to inefficient protein-protein interactions between human constant regions and mouse B cell receptors and Fc receptors.<sup>8-10</sup> The hampered function led to reduced receptor signaling, limited affinity maturation, antibodies switching between IgM, IgD, IgG, IgA or IgE subtypes, and inefficient B cell differentiation into mature antibody-secreting plasma B cells.

Limited antibody production can result from insertion of human genes that lack necessary regions for controlling gene expression—such as enhancers, switch regions and regulatory elements—for efficient Ig transcription and recombination.<sup>11-13</sup>

## Diplomatic immunity

To boost the efficacy of their mouse platforms, Kymab and Regeneron each independently engineered animals that retained a functional immune system and contained a larger human Ig sequence component than previous transgenic mice.

Regeneron's approach preserved the intact murine constant regions and swapped mouse variable regions for their human equivalents using large bacterial artificial chromosome-based targeting vectors.

The new version included a much more complete replacement of mouse regions. Regeneron engineered mouse embryonic stem cells (ESCs) that were used to produce mice in which 6 Mb of mouse genomic sequence had been replaced with 1.4 Mb of human genomic sequence.

Regeneron immunized transgenic mice and wild-type mice with the extracellular domain of the human IL-6 receptor (CD126), and both sets of mice mounted strong antibody responses with similar titer ranges and IgG isotypes, suggesting that humoral response and class switching are similar in both types of mice. In short, the immune systems of the mice were similar.

Importantly, wild-type mice produced antibodies that had mouse variable and constant regions, and transgenic mice produced antibodies that had human variable and mouse constant regions.

The lead high-affinity anti-CD126 antibody from the transgenic mice was reformatted by replacement of mouse Ig constant regions with human Ig constant regions to make a fully human antibody. The CD126 mAb, now called sarilumab (REGN8), is in Phase III testing to treat rheumatoid arthritis and Phase II testing for uveitis.

Data were published in the *Proceedings of the National Academy of Sciences*.

According to Andrew Murphy, SVP of research at Regeneron, “the company's 15 mAbs discovered in the VelocImmune mice have entered into clinical development and have all progressed very rapidly—in as little as 18 months—which are time frames that significantly surpass industry standards.”

**“The human immunoglobulin variable sequences are efficiently rearranged, and their linkage to endogenous immunoglobulin mouse constant sequences provides a flawless interplay with the endogenous signaling machinery. This means that B cell development appears to be normal and class switch with somatic hypermutation is maintained.”**

—Roland Buelow,  
Recombinant Antibody  
Technology Ltd.

Kymab used large bacterial artificial chromosome-based targeting vectors and added the genes encoding the human variable regions to the mouse genome. Rather than deleting mouse sequence, the company generated large chromosomal inversions of the mouse variable regions to block potential interference between the two sets of genes.

In total, Kymab's engineered mouse ESCs contained an extra 2.7 Mb of human variable Ig genomic sequences.

The Kymab team immunized its transgenic mice with a human CD40 ligand (CD40LG; CD40L; CD154) antigen or a *Staphylococcus aureus*  $\alpha$ -hemolysin (aHL) antigen. The resulting antibodies were at least as potent as the anti-CD40L humanized antibody 5C8 or the anti-aHL human antibody KBSA301.

**Biogen Idec Inc.**'s 5C8 is in Phase I testing to treat systemic lupus erythematosus. **Kenta Biotech Ltd.**'s KBSA301 is in Phase I/II testing

to treat pneumonia and in Phase I testing to treat *Staphylococcus* infection.

Results were published in *Nature Biotechnology*. Kymab did not respond to interview requests.

## Constant presence

According to Hans de Haard, CSO of **arGEN-X B.V.**, the real advance in these studies is that new transgenic mouse systems have been generated with a more normal and functional immune system capable of introducing somatic hypermutations and producing antibody amounts comparable to those seen in wild-type mice.

“The human immunoglobulin variable sequences are efficiently rearranged, and their linkage to endogenous immunoglobulin mouse constant sequences provides a flawless interplay with the endogenous signaling machinery,” said Roland Buelow, CEO of both **Recombinant Antibody Technology Ltd.** (RAT) and **Open Monoclonal Technology Inc.** (OMT). “This means that B cell development appears to be normal and class switch with somatic hypermutation is maintained.”

RAT produces large recombinant gene loci using artificial bacterial

and yeast chromosomes and works with OMT to produce mouse (OmniMouse) and rat (OmniRat and OmniFlic) platforms for human therapeutic antibody discovery.

de Haard said he has looked at the sequences of both sets of antibodies, and “comparison of the sequences of these new leads with antibodies from the first-generation transgenic mouse systems demonstrates to me that these are indeed better affinity matured by the animals’ immune system” than previous mouse-derived human antibodies.

arGEN-X uses llamas for human therapeutic antibody discovery. The company’s ARGX-110, a human anti-CD70 (CD27L) antibody, and ARGX-111, a human antibody against c-Met proto-oncogene (MET; HGFR), are both in Phase Ib testing for hematologic malignancies and solid tumors.

An unanswered question is whether increasing the number of transgenic human Ig variable regions will generate greater diversity in human therapeutic antibodies.

“It is debatable if inclusion of more, or indeed all, variable genes is desirable or distractive,” said Marianne Brüggemann, director of research and head of the antibody development at both RAT and OMT. “For example, is there really an advantage for including over 20 near-identical variable genes, or will this negatively bias immune diversity?”

“In terms of whether these advances will translate to increased numbers of therapeutic antibodies going into clinical trials, that remains to be seen,” de Haard told *SciBX*.

Both Regeneron and Kymab have patented their respective platforms. Last year, Regeneron filed claims in the English Court alleging that Kymab infringes Regeneron’s European patent EP1360287, which covers methods to genetically modify a mouse to make antibodies with human variable regions. Kymab has said it will defend on the grounds of noninfringement and invalidity of the patent.

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Published online May 1, 2014

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e-mail: [andrew.murphy@regeneron.com](mailto:andrew.murphy@regeneron.com)  
**Contact:** George D. Yancopoulos, same affiliation as above  
e-mail: [george@regeneron.com](mailto:george@regeneron.com)
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**Contact:** Andrew J. Murphy, Regeneron Pharmaceuticals Inc., Tarrytown, N.Y.  
e-mail: [andrew.murphy@regeneron.com](mailto:andrew.murphy@regeneron.com)  
**Contact:** George D. Yancopoulos, same affiliation as above  
e-mail: [george@regeneron.com](mailto:george@regeneron.com)
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**Contact:** Allan Bradley, Kymab Ltd., Cambridge, U.K.  
e-mail: [abradley@kymab.com](mailto:abradley@kymab.com)
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## COMPANIES AND INSTITUTIONS MENTIONED

**arGEN-X B.V.**, Rotterdam, the Netherlands  
**Biogen Idec Inc.** (NASDAQ:BIIB), Weston, Mass.  
**Kenta Biotech Ltd.**, Schlieren, Switzerland  
**Kymab Ltd.**, Cambridge, U.K.  
**Open Monoclonal Technology Inc.**, Palo Alto, Calif.  
**Recombinant Antibody Technology Ltd.**, Cambridge, U.K.  
**Regeneron Pharmaceuticals Inc.** (NASDAQ:REGN), Tarrytown, N.Y.



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## 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>				
Asthma	Serum/ glucocorticoid regulated kinase 1 (SGK1)	Cell culture and mouse studies suggest inhibiting SGK1 could help treat asthma. In a mouse model of allergic asthma, T cell-specific knockout of <i>Sgk1</i> led to an antigen-induced T helper type 1 (Th1) cell response and decreased levels of allergic markers, whereas wild-type mice developed a pathogenic Th2 cell response. Mice with the T cell-specific <i>Sgk1</i> knockout were protected from allergen-induced inflammatory lung disease. Next steps could include testing small molecule inhibitors of SGK1 in animal models of allergic asthma.  <b>SciBX 7(17); doi:10.1038/scibx.2014.480</b> <b>Published online May 1, 2014</b>	Patent and licensing status unavailable	Heikamp, E.B. <i>et al. Nat. Immunol.</i> ; published online April 6, 2014; doi:10.1038/ni.2867 <b>Contact:</b> Jonathan D. Powell, The Johns Hopkins University School of Medicine, Baltimore, Md. e-mail: <a href="mailto:poweljo@jhmi.edu">poweljo@jhmi.edu</a>
Lupus	Calcium calmodulin- dependent protein kinase IV (CAMK4)	Studies in human samples and mice suggest inhibiting CAMK4 could help treat lupus. T helper type 17 (Th17) cells are a subset of IL-17-producing T cells that drive multiple autoimmune diseases including lupus. In multiple mouse models of lupus, <i>Camk4</i> knockout or inhibition with a small molecule decreased disease severity and the number of IL-17-producing T cells compared with no alteration or inhibition. In T cells from healthy donors and patients with lupus, siRNA against or pharmacological inhibition of <i>CAMK4</i> decreased IL-17 production compared with control siRNA or no treatment. Next steps include developing a more specific CAMK4 inhibitor and extending the findings to other autoimmune indications including multiple sclerosis (MS), rheumatoid arthritis (RA), glomerulonephritis and vasculitis.  <b>SciBX 7(17); doi:10.1038/scibx.2014.481</b> <b>Published online May 1, 2014</b>	Patent application filed by Beth Israel Deaconess Medical Center; available for partnering <b>Contact:</b> Stanley Mah, Beth Israel Deaconess Medical Center, Boston, Mass. e-mail: <a href="mailto:smah@bidmc.harvard.edu">smah@bidmc.harvard.edu</a>	Koga, T. <i>et al. J. Clin. Invest.</i> ; published online March 25, 2014; doi:10.1172/JCI73411 <b>Contact:</b> George C. Tsokos, Harvard Medical School, Boston, Mass. e-mail: <a href="mailto:gtsokos@bidmc.harvard.edu">gtsokos@bidmc.harvard.edu</a> <b>Contact:</b> José C. Crispín, same affiliation as above e-mail: <a href="mailto:jcrispin@bidmc.harvard.edu">jcrispin@bidmc.harvard.edu</a>
<b>Cancer</b>				
Cancer	c-Myc (MYC)	<i>In vitro</i> studies suggest blocking both full-length MYC and its N-terminal cleavage product could help treat cancer. MYC upregulation not only promotes cell proliferation and is linked to cancer but also can induce apoptosis under cellular stress conditions. In human colon cancer cell lines, stress conditions promoted conversion of MYC to its cytoplasmic N-terminal cleavage product. In colon cancer cells, vector-induced overexpression of the cleavage product resulted in increased survival under nutrient deprivation, anchorage-independent cell growth and resistance to chemotherapy drugs compared with wild-type expression. Next steps could include assessing the effects of the cleavage product in animal models of cancer.  <b>SciBX 7(17); doi:10.1038/scibx.2014.482</b> <b>Published online May 1, 2014</b>	Patent and licensing status unavailable	Conacci-Sorrell, M. <i>et al. Genes Dev.</i> ; published online April 1, 2014; doi:10.1101/gad.231894.113 <b>Contact:</b> Robert N. Eisenman, Fred Hutchinson Cancer Research Center, Seattle, Wash. e-mail: <a href="mailto:eisenman@fhcrc.org">eisenman@fhcrc.org</a>

## This week in therapeutics (continued)

Indication	Target/marker/pathway	Summary	Licensing status	Publication and contact information
Cancer	CTLA-4 (CD152); inducible T cell co-stimulator (ICOS)	<p>Mouse studies suggest combining anti-CTLA-4 antibodies plus vaccines that increase ICOS could help treat various cancers. In a mouse model of melanoma, inhibition of Ctl-4 increased expression of Icos on intratumoral T cells compared with no inhibition. In mice, an anti-Ctla-4 mAb plus a tumor cell vaccine made from irradiated melanoma cells expressing an Icos ligand resulted in an antitumor response that prevented melanoma tumor establishment after secondary challenge and caused a fourfold increase in rejection of intradermal melanoma tumors compared with anti-Ctla-4 mAb alone. The combined strategy also caused rejection of prostate tumors in mice. Next steps could include identifying other therapeutic methods to increase ICOS signaling.</p> <p>Bristol-Myers Squibb Co. markets the anti-CTLA-4 mAb Yervoy ipilimumab to treat melanoma. At least three other companies have CTLA-4-targeted agents in Phase II or earlier testing to treat various cancers.</p> <p><b>SciBX 7(17); doi:10.1038/scibx.2014.483</b> Published online May 1, 2014</p>	Patent and licensing status unavailable	<p>Fan, X. <i>et al. J. Exp. Med.</i>; published online March 31, 2014; doi:10.1084/jem.20130590</p> <p><b>Contact:</b> James P. Allison, The University of Texas MD Anderson Cancer Center, Houston, Texas e-mail: <a href="mailto:jallison@mdanderson.org">jallison@mdanderson.org</a></p> <p><b>Contact:</b> Padmanee Sharma, same affiliation as above e-mail: <a href="mailto:padsharma@mdanderson.org">padsharma@mdanderson.org</a></p>
Cancer	Integrin $\alpha_v\beta_3$ (CD51/CD61)	<p><i>In vitro</i> studies have identified selective integrin <math>\alpha_v\beta_3</math> antagonists that could be useful for treating cancer. Synthesis of arginine-glycine-aspartic (RGD) acid peptidomimetics based on a <math>\beta</math>-homotyrosine scaffold yielded integrin <math>\alpha_v\beta_3</math> antagonists with EC<sub>50</sub> values in the low nanomolar or subnanomolar range and good selectivity for integrin <math>\alpha_v\beta_3</math> over integrin <math>\alpha_3\beta_1</math>. Next steps could include comparing the RGD acid peptidomimetics with Merck KGaA's cilengitide in animal models.</p> <p>Cilengitide is a cyclic peptide angiogenesis inhibitor that potently blocks integrin <math>\alpha_v\beta_3</math> but also has activity against the related integrin <math>\alpha_3\beta_1</math>, which prevents selective targeting. The molecule is in Phase II testing to treat head and neck cancer and lung cancer. At least five other companies have integrin <math>\alpha_v\beta_3</math>-targeting compounds in Phase II testing or earlier to treat various cancers.</p> <p><b>SciBX 7(17); doi:10.1038/scibx.2014.484</b> Published online May 1, 2014</p>	Patent and licensing status unavailable	<p>Neubauer, S. <i>et al. J. Med. Chem.</i>; published online March 23, 2014; doi:10.1021/jm500092w</p> <p><b>Contact:</b> Horst Kessler, Technical University Munich, Munich, Germany e-mail: <a href="mailto:kessler@tum.de">kessler@tum.de</a></p>

## This week in therapeutics (continued)

Indication	Target/marker/ pathway	Summary	Licensing status	Publication and contact information
Cancer	p53	<p><i>In vitro</i> and cell-based studies suggest combining an inhibitor of nonsense-mediated RNA decay and a promoter of premature stop-codon read-through could help treat cancer. Virtual library screening and <i>in vitro</i> testing identified several nonsense-mediated RNA decay inhibitors with nanomolar potency. In human cancer cell lines harboring premature stop-codon mutations in p53, one inhibitor increased mutant p53 mRNA levels compared with vehicle. In the cancer cell lines, the inhibitor and a research compound that promotes premature stop-codon read-through synergistically increased functional p53 levels and cell death compared with either agent alone. Next steps include optimizing the nonsense-mediated RNA decay inhibitors.</p> <p>PTC Therapeutics Inc.'s Translarna ataluren (formerly PTC124), a small molecule that facilitates complete translation of proteins containing nonsense mutations, is under EMA review to treat muscular dystrophy. The compound also is in Phase III testing to treat cystic fibrosis (CF) and Phase II trials to treat methylmalonic acidemia.</p> <p><b>SciBX 7(17); doi:10.1038/scibx.2014.485</b> Published online May 1, 2014</p>	Patented by New York University; unlicensed; available for partnering	<p>Martin, L. <i>et al. Cancer Res.</i>; published online March 24, 2014; doi:10.1158/0008-5472.CAN-13-2235  <b>Contact:</b> Lawrence B. Gardner, New York University School of Medicine, New York, N.Y.            e-mail:  <a href="mailto:lawrence.gardner@med.nyu.edu">lawrence.gardner@med.nyu.edu</a></p>
Cancer	Receptor tyrosine kinase (RTK); VEGF-A	<p>Mouse and cell culture studies identified apratoxin analogs that could be useful for treating cancer. Apratoxins are cyanobacteria-derived compounds that downregulate expression of genes including RTKs. In a human colorectal cancer cell line, the analogs reduced viability and VEGF-A secretion with single-digit nanomolar to subnanomolar IC<sub>50</sub> values. In a mouse xenograft model of human colorectal cancer, injection of an apratoxin analog caused a dose-dependent decrease in tumor growth compared with vehicle injection. Next steps could include evaluating the lead analog in additional mouse models of cancer.</p> <p><b>SciBX 7(17); doi:10.1038/scibx.2014.486</b> Published online May 1, 2014</p>	Patent and licensing status unavailable	<p>Chen, Q.-Y. <i>et al. J. Med. Chem.</i>; published online March 24, 2014; doi:10.1021/jm4019965  <b>Contact:</b> Hendrik Luesch, University of Florida, Gainesville, Fla.            e-mail:  <a href="mailto:luesch@cop.ufl.edu">luesch@cop.ufl.edu</a></p>
Cancer	Retinoid X receptor- $\alpha$ (RXRA; RXR $\alpha$ )	<p><i>In vitro</i> and mouse studies identified derivatives of the generic NSAID sulindac that specifically inhibit RXR<math>\alpha</math> and could help treat cancer. Sulindac derivatives were designed to block the binding between N-terminal-truncated RXR<math>\alpha</math> and phosphoinositide 3-kinase regulatory subunit 1<math>\alpha</math> (PIK3R1; p85<math>\alpha</math>) to inhibit downstream protein kinase B (PKB; PKBA; AKT; AKT1) signaling. In human lung, breast and prostate cancer cell lines, the two lead sulindac derivatives caused greater apoptosis than sulindac. In a mouse xenograft model of hepatocellular carcinoma, the derivatives each decreased tumor growth compared with vehicle. Next steps include safety and toxicity studies of the derivatives.</p> <p><b>SciBX 7(17); doi:10.1038/scibx.2014.487</b> Published online May 1, 2014</p>	Patent application filed; available for licensing	<p>Chen, L. <i>et al. Chem. Biol.</i>; published online April 2, 2014; doi:10.1016/j.chembiol.2014.02.017  <b>Contact:</b> Ying Su, Sanford-Burnham Medical Research Institute, La Jolla, Calif.            e-mail:  <a href="mailto:ysu@sanfordburnham.org">ysu@sanfordburnham.org</a>  <b>Contact:</b> Xiao-kun Zhang, same affiliation as above            e-mail:  <a href="mailto:xzhang@sanfordburnham.org">xzhang@sanfordburnham.org</a></p>

## This week in therapeutics (continued)

Indication	Target/marker/pathway	Summary	Licensing status	Publication and contact information
Chronic myelogenous leukemia (CML)	IL-1 receptor-like 1 (IL1RL1; ST2); IL-33 (NF-HEV)	<p>Mouse and cell culture studies suggest inhibiting IL-33 signaling could help treat Gleevec imatinib-resistant CML. CD34<sup>+</sup> cells from patients with CML had surface expression of ST2 and greater proliferation in response to IL-33 than CD34<sup>+</sup> cells from healthy subjects. IL-33 is an activating ligand for ST2. In patient-isolated CD34<sup>+</sup> cells, IL-33 blocked the effect of Gleevec on proliferation. Next steps could include evaluating IL-33 inhibitors in combination with Gleevec in models of Gleevec-resistant CML. Novartis AG markets Gleevec, a BCR-ABL tyrosine kinase inhibitor, to treat CML, acute lymphoblastic leukemia (ALL) and gastrointestinal stromal tumors (GISTs).</p> <p>AnaptysBio Inc.'s ANB020, an anti-IL-33 antibody, is in discovery for various inflammatory conditions.</p> <p><b>SciBX 7(17); doi:10.1038/scibx.2014.488</b> Published online May 1, 2014</p>	Patent and licensing status unavailable	<p>Levescot, A. <i>et al. Cancer Res.</i>; published online March 27, 2014; doi:10.1158/0008-5472.CAN-13-2797 <b>Contact:</b> Andre Herbelin, Institut National de la Santé et de la Recherche Médicale (INSERM), Poitiers, France e-mail: <a href="mailto:andre.herbelin@inserm.fr">andre.herbelin@inserm.fr</a></p>
Colorectal cancer	Jumonji domain containing 6 (JMJD6)	<p>Mouse and <i>in vitro</i> studies suggest inhibiting JMJD6 signaling could be useful for treating colon cancer. <i>In vitro</i>, JMJD6 acted as an <math>\alpha</math>-ketoglutarate- and Fe(II)-dependent lysyl hydroxylase, which catalyzes hydroxylation of the tumor suppressor p53 to decrease its transcriptional activity. In human colon cancer cell lines and a mouse xenograft model of colorectal cancer, siRNA against <i>Jmjd6</i> increased p53 activity and apoptosis and decreased tumor growth compared with control siRNA. Next steps could include screening for inhibitors of JMJD6.</p> <p><b>SciBX 7(17); doi:10.1038/scibx.2014.489</b> Published online May 1, 2014</p>	Patent and licensing status unavailable	<p>Wang, F. <i>et al. PLoS Biol.</i>; published online March 25, 2014; doi:10.1371/journal.pbio.1001819 <b>Contact:</b> Yongfeng Shang, Peking University Health Science Center, Beijing, China e-mail: <a href="mailto:yshang@hsc.pku.edu.cn">yshang@hsc.pku.edu.cn</a> <b>Contact:</b> Luyang Sun, same affiliation as above e-mail: <a href="mailto:luyang_sun@hsc.pku.edu.cn">luyang_sun@hsc.pku.edu.cn</a></p>
Lymphoma	IL-2	<p>Mouse studies suggest a complex composed of an IL-2 mAb and IL-2 could help improve the ability of cancer vaccines to prevent relapse in patients with lymphoma. In mice with minimal residual lymphoma, a cancer vaccine combined with i.p. infusion of the IL-2 mAb-IL-2 complex resulted in 60% of the animals surviving for more than 100 days versus 20% for vaccine alone and 0% for no treatment. Next steps include developing other cytokine-based compounds and testing them with the vaccine in humanized mouse models of cancer.</p> <p>Heat Biologics Inc. uses its Immune Pan-Antigen Cytotoxic Therapy (ImPACT) technology platform to create vaccines adjuvanted with allogeneic cancer cells that continually secrete heat shock 90 kDa protein <math>\beta</math>1 (Hsp90B1; GP96; GRP94). The company's most advanced ImPACT cancer vaccine is HS-110, which is in Phase II testing for non-small cell lung cancer (NSCLC).</p> <p><b>SciBX 7(17); doi:10.1038/scibx.2014.490</b> Published online May 1, 2014</p>	Cancer vaccine patented; licensed to Heat Biologics	<p>Newman, R.G. <i>et al. Blood</i>; published online March 31, 2014; doi:10.1182/blood-2013-08-520775 <b>Contact:</b> Robert B. Levy, University of Miami Miller School of Medicine, Miami, Fla. e-mail: <a href="mailto:rlevy@med.miami.edu">rlevy@med.miami.edu</a></p>

## This week in therapeutics (continued)

Indication	Target/marker/ pathway	Summary	Licensing status	Publication and contact information
Non-small cell lung cancer (NSCLC)	IL-17	<p>Mouse studies suggest blocking IL-17 could help treat or prevent inflammatory chronic obstructive pulmonary disease (COPD)-associated NSCLC. In a mouse model of early NSCLC, inoculation of COPD-generating lysates from <i>Haemophilus influenza</i> increased tumor growth, which was associated with higher T helper type 17 (Th17) cell numbers, compared with no inoculation. In lysate-treated mice with NSCLC, <i>Il-17</i> knockout decreased tumor growth compared with <i>Il-17f</i> knockout. Antibody-mediated depletion of IL-17-recruited myeloid cells also decreased tumor growth compared with no alteration. Next steps include investigating other reagents that could block Th17 cells such as IL-23-specific antibodies or RAR-related orphan receptor C thymus-specific isoform (ROR<math>\gamma</math>2; ROR<math>\gamma</math>T) inhibitors. Brodalumab, a humanized mAb against IL-17 receptor (IL17R; IL17RA) from Amgen Inc. and partners AstraZeneca plc and Kyowa Hakko Kirin Co. Ltd., is in Phase III testing to treat psoriasis and Phase II trials to treat asthma, psoriatic arthritis and inflammatory diseases.</p> <p>At least eight other companies have compounds that block IL-17 signaling in Phase II or earlier development to treat various autoimmune and inflammatory diseases.</p> <p><b>SciBX 7(17); doi:10.1038/scibx.2014.491</b> Published online May 1, 2014</p>	Unpatented; licensing status not applicable	<p>Chang, S.H. <i>et al. Proc. Natl. Acad. Sci. USA</i>; published online March 31, 2014; doi:10.1073/pnas.1319051111 <b>Contact:</b> Seyed Javad Moghaddam, The University of Texas MD Anderson Cancer Center, Houston, Texas e-mail: <a href="mailto:smoghadd@mdanderson.org">smoghadd@mdanderson.org</a> <b>Contact:</b> Seon Hee Chang, same affiliation as above e-mail: <a href="mailto:shchang@mdanderson.org">shchang@mdanderson.org</a></p>
Non-small cell lung cancer (NSCLC)	Lactate dehydrogenase A (LDHA); K-Ras (KRAS); epidermal growth factor receptor 1 (EGFR1; HER1; ErbB1)	<p>Mouse studies suggest inhibiting LDHA could help treat <i>KRAS</i>- and <i>EGFR1</i>-mutant NSCLC. LDHA catalyzes a key step in anaerobic glycolysis, which NSCLC relies upon for growth and metastasis. In normal mice, injection of a human <i>KRAS</i>-mutant NSCLC cell line expressing an <i>LDHA</i> shRNA resulted in fewer metastatic lesions than injection of unmodified cells. In mice with NSCLC xenograft tumors harboring activating mutations in <i>KRAS</i> or <i>EGFR1</i>, <i>Ldha</i> deficiency decreased glycolytic metabolite levels and tumor growth compared with unmodified <i>Ldha</i> expression. Results of <i>Ldha</i> deficiency in other tumor types will be reported in an upcoming publication.</p> <p><b>SciBX 7(17); doi:10.1038/scibx.2014.492</b> Published online May 1, 2014</p>	Unpatented; licensing status not applicable	<p>Xie, H. <i>et al. Cell Metab.</i>; published online April 10, 2014; doi:10.1016/j.cmet.2014.03.003 <b>Contact:</b> Pankaj Seth, Beth Israel Deaconess Medical Center, Boston, Mass. e-mail: <a href="mailto:pseth@bidmc.harvard.edu">pseth@bidmc.harvard.edu</a> <b>Contact:</b> Teresa W.M. Fan, University of Louisville, Louisville, Ky. e-mail: <a href="mailto:teresa.fan@uky.edu">teresa.fan@uky.edu</a></p>
<b>Endocrine/metabolic disease</b>				
Obesity	Amylase $\alpha$ 1A (AMY1A); AMY1B; AMY1C	<p>Genetic studies identified an association between copy number variants of the salivary amylase genes and obesity that could lead to new therapeutics. Amylase is involved in salivary digestion of starch. In a genetic association study of adipose tissue from 149 families and in validation cohorts of more than 6,000 individuals, low copy numbers of the <i>AMY1</i> gene cluster, which encompasses <i>AMY1A</i>, <i>AMY1B</i> and <i>AMY1C</i>, correlated with high BMI and obesity. In serum from morbidly obese individuals, salivary AMY1 protein levels were lower than those in healthy controls. Next steps include establishing the mechanistic relationship between AMY1 and obesity.</p> <p><b>SciBX 7(17); doi:10.1038/scibx.2014.493</b> Published online May 1, 2014</p>	Patent and licensing status unavailable	<p>Falchi, M. <i>et al. Nat. Genet.</i>; published online March 30, 2014; doi:10.1038/ng.2939 <b>Contact:</b> Philippe Froguel, Imperial College London, London, U.K. e-mail: <a href="mailto:p.froguel@imperial.ac.uk">p.froguel@imperial.ac.uk</a> <b>Contact:</b> Mario Falchi, same affiliation as above e-mail: <a href="mailto:m.falchi@imperial.ac.uk">m.falchi@imperial.ac.uk</a></p>

## This week in therapeutics (continued)

Indication	Target/marker/ pathway	Summary	Licensing status	Publication and contact information
<b>Genitourinary disease</b>				
Polycystic ovary syndrome (PCOS)	DENN/MADD domain containing 1A (DENND1A)	Patient and cell culture studies suggest a DENND1A isoform could be a marker and target for PCOS. Past studies have identified <i>DENND1A</i> as a risk locus for PCOS, which is caused by excess androgen secretion by a subset of ovarian follicle cells called thecal cells. In urine samples from patients with PCOS, levels of exosomes containing RNA of a truncated <i>DENND1A</i> isoform were higher than those in samples from healthy women. In patient thecal cells, a rabbit antibody or shRNA against the truncated <i>DENND1A</i> isoform decreased the induction of androgen-producing enzymes and consequent androgen production compared with an inactive control IgG or scrambled control shRNA. Ongoing work includes developing a PCOS diagnostic based on urine levels of <i>DENND1A</i> isoform RNA.  <b>SciBX 7(17); doi:10.1038/scibx.2014.494</b> <b>Published online May 1, 2014</b>	Patent application filed by Pennsylvania State University and Virginia Commonwealth University; available for licensing	McAllister, J.M. <i>et al. Proc. Natl. Acad. Sci. USA</i> ; published online March 31, 2014; doi:10.1073/pnas.1400574111 <b>Contact:</b> Jan M. McAllister, Pennsylvania State University Hershey College of Medicine, Hershey, Pa. e-mail: <a href="mailto:jmcallister@psu.edu">jmcallister@psu.edu</a>
<b>Hepatic disease</b>				
Liver disease	Sirtuin 7 (SIRT7)	Mouse studies suggest inhibiting SIRT7 could help treat hepatic steatosis. In mice, <i>Sirt7</i> knockout decreased high-fat diet-induced hepatic lipid accumulation, hepatic triglyceride levels and cholesterol levels compared with no alteration. In the mice, <i>Sirt7</i> knockout also attenuated high-fat diet-induced weight gain and improved insulin and glucose tolerance. Next steps include understanding the role of SIRT7 in metabolic tissues beyond the liver and validating it as a therapeutic target.  <b>SciBX 7(17); doi:10.1038/scibx.2014.495</b> <b>Published online May 1, 2014</b>	Unpatented; licensing status not applicable	Yoshizawa, T. <i>et al. Cell Metab.</i> ; published online April 1, 2014; doi:10.1016/j.cmet.2014.03.006 <b>Contact:</b> Kazuya Yamagata, Kumamoto University, Kumamoto, Japan e-mail: <a href="mailto:k-yamaga@kumamoto-u.ac.jp">k-yamaga@kumamoto-u.ac.jp</a>
<b>Infectious disease</b>				
HIV/AIDS	Not applicable	<i>In vitro</i> studies suggest inducing an IgG3 response against HIV antigens could help create protective immunity against infection. In a clinical trial, Sanofi's ALVAC HIV vaccine and a bivalent clade B/E recombinant gp120 immunogen induced an antigen-specific IgG3 response and partial protective immunity, whereas another vaccination regimen that induced a weaker IgG3 response did not result in protective immunity. Next steps could include developing a vaccination strategy that induces a persistent IgG3 response. ALVAC HIV is in Phase III testing.  <b>SciBX 7(17); doi:10.1038/scibx.2014.496</b> <b>Published online May 1, 2014</b>	Patent and licensing status unavailable	Yates, N.L. <i>et al. Sci. Transl. Med.</i> ; published online March 19, 2014; doi:10.1126/scitranslmed.3007730 <b>Contact:</b> Georgia D. Tomaras, Duke University, Durham, N.C. e-mail: <a href="mailto:gdt@duke.edu">gdt@duke.edu</a>

## This week in therapeutics (continued)

Indication	Target/marker/ pathway	Summary	Licensing status	Publication and contact information
<b>Neurology</b>				
Huntington's disease (HD)	Potassium channel Kir4.1 (KCNJ10)	<p>Mouse studies suggest increasing Kir4.1 expression could help treat HD. In mouse models of HD, striatal astrocytes were more depolarized and had lower Kir4.1 currents than those in wild-type mice. In a mouse model of HD, viral vector-mediated expression of Kir4.1 in astrocytes prolonged survival and improved motor properties; it also decreased striatal astrocyte depolarization and increased Kir4.1 currents compared with viral vector-mediated expression of a control protein. Next steps could include optimizing viral vectors for therapeutic delivery of Kir4.1 or designing compounds to augment channel activity.</p> <p><b>SciBX 7(17); doi:10.1038/scibx.2014.497</b>  <b>Published online May 1, 2014</b></p>	Unpatented; licensing status not applicable	<p>Tong, X. <i>et al. Nature Neurosci.</i>; published online March 30, 2014; doi:10.1038/nn.3691  <b>Contact:</b> Baljit S. Khakh, University of California, Los Angeles, Calif.  e-mail: <a href="mailto:bkhakh@mednet.ucla.edu">bkhakh@mednet.ucla.edu</a>  <b>Contact:</b> Michael V. Sofroniew, same affiliation as above  e-mail: <a href="mailto:sofroniew@mednet.ucla.edu">sofroniew@mednet.ucla.edu</a></p>
Spinal cord injury (SCI)	Chondroitin sulfate proteoglycan (CSPG)	<p>Rat studies suggest lentivirus-delivered, mammalian-optimized chondroitinase ABC (ChABC) could help treat SCI. Levels of extracellular matrix-associated CSPGs increase and inhibit repair processes following SCI. In rats with spinal cord contusions, spinal injections of lentivirus expressing the optimized ChABC promoted more digestion of CSPGs than injections of bacterial ChABC protein. In these mice, lentivirus delivery of the optimized ChABC increased the number of surviving neurons at injury centers compared with control virus delivery or no treatment and improved conduction of spinal axons and performance in motor tasks. Next steps could include assessing the effect of long-term ChABC expression on pain sensitivity and developing inducible expression systems for the optimized enzyme.</p> <p><b>SciBX 7(17); doi:10.1038/scibx.2014.498</b>  <b>Published online May 1, 2014</b></p>	Patent and licensing status unavailable	<p>Bartus, K. <i>et al. J. Neurosci.</i>; published online April 2, 2014; doi:10.1523/JNEUROSCI.4369-13.2014  <b>Contact:</b> Elizabeth J. Bradbury, King's College London, London, U.K.  e-mail: <a href="mailto:elizabeth.bradbury@kcl.ac.uk">elizabeth.bradbury@kcl.ac.uk</a></p>
Stroke	Arachidonate 15-lipoxygenase (ALOX15; 15-LOX)	<p><i>In vitro</i> and mouse studies suggest a new class of ALOX15 inhibitors could help treat stroke. Chemical synthesis and <i>in vitro</i> testing of oxazole-4-carbonitrile analogs identified a lead compound that inhibited ALOX15 with a nanomolar IC<sub>50</sub> value. In a mouse neuron-based assay of Alox15-mediated oxidative stress, the lead compound caused a dose-dependent decrease in cell death compared with no treatment. In mouse models of ischemic stroke, i.p. injection of the lead compound two hours after ischemia decreased infarct size compared with vehicle injection. Ongoing work includes optimizing the lead compound and testing it in additional mouse models of stroke and other cerebrovascular diseases.</p> <p><b>SciBX 7(17); doi:10.1038/scibx.2014.499</b>  <b>Published online May 1, 2014</b></p>	Patent application filed by Massachusetts General Hospital; available for licensing	<p>Holman, T.R. <i>et al. J. Med. Chem.</i>; published online March 31, 2014; doi:10.1021/jm401915r  <b>Contact:</b> Klaus van Leyen, Harvard Medical School, Charlestown, Mass.  e-mail: <a href="mailto:klaus_vanleyen@hms.harvard.edu">klaus_vanleyen@hms.harvard.edu</a>  <b>Contact:</b> David J. Maloney, National Institutes of Health, Bethesda, Md.  e-mail: <a href="mailto:maloneyd@mail.nih.gov">maloneyd@mail.nih.gov</a>  <b>Contact:</b> Theodore Russell Holman, University of California, Santa Cruz, Calif.  e-mail: <a href="mailto:tholman@chemistry.ucsc.edu">tholman@chemistry.ucsc.edu</a></p>

## This week in therapeutics (continued)

Indication	Target/marker/ pathway	Summary	Licensing status	Publication and contact information
<b>Other</b>				
Cushing's disease	Protein kinase cAMP-dependent catalytic- $\alpha$ (PRKACA) L205R	Genetic sequencing studies identified an activating <i>PRKACA</i> mutation in Cushing's disease that could help model the disorder. In 49 adrenocortical tumor samples from patients with Cushing's disease, the somatic <i>PRKACA</i> L205R mutation was found in 55.1% of tumors and specifically in 69.1% of the benign adrenocortical adenoma tumor subset. In human cells, overexpression of <i>PRKACA</i> L205R increased phosphorylation of <i>PRKACA</i> substrates compared with wild-type <i>PRKACA</i> expression, suggesting it is an activating mutation. Next steps include developing a transgenic mouse model of Cushing's disease based on the findings.  <b>SciBX 7(17); doi:10.1038/scibx.2014.500</b> <b>Published online May 1, 2014</b>	Findings unpatented; available for licensing to diagnose subtypes of Cushing's disease	Cao, Y. <i>et al. Science</i> ; published online April 3, 2014; doi:10.1126/science.1249480 <b>Contact:</b> Guang Ning, Shanghai Jiao-Tong University School of Medicine, Shanghai, China e-mail: <a href="mailto:guangning@medmail.com.cn">guangning@medmail.com.cn</a> <b>Contact:</b> Weiqing Wang, same affiliation as above e-mail: <a href="mailto:wqingw@hotmail.com">wqingw@hotmail.com</a> <b>Contact:</b> Jun Wang, BGI Shanghai and BGI Shenzhen, Shenzhen, China e-mail: <a href="mailto:wangj@genomics.org.cn">wangj@genomics.org.cn</a>
<b>Pulmonary disease</b>				
Pulmonary disease	Src; tuberous sclerosis complex tumor suppressor 2 (TSC2)	Studies in patient samples, cell culture and mice suggest inhibiting Src kinase activity could help treat the progressive cystic lung disease lymphangiomyomatosis (LAM). LAM commonly affects patients who have mutations in <i>TSC2</i> . In samples from patients with LAM and in a <i>Tsc2</i> -deficient rat fibroblast cell line, Src phosphorylation levels were greater than those in normal samples and wild-type fibroblasts. In mice, the Src kinase inhibitor saracatinib decreased lung colonization by <i>Tsc2</i> -deficient rat fibroblasts injected into the peritoneum compared with vehicle. Next steps include clinical trials to evaluate Src kinase inhibitors to treat LAM. AstraZeneca plc's saracatinib, a dual inhibitor of Src and BCR-ABL tyrosine kinases, has completed a Phase IIb trial in ovarian cancer. Bristol-Myers Squibb Co. and Otsuka Pharmaceutical Co. Ltd. market Sprycel dasatinib, a small molecule inhibitor of BCR-ABL and Src kinases, to treat acute lymphoblastic leukemia (ALL) and chronic myelogenous leukemia (CML). Pfizer Inc. markets Bosulif bosutinib, a dual inhibitor of BCR-ABL and Src kinases, to treat CML. At least six other companies have Src kinase-inhibiting drug candidates in Phase II testing or earlier to treat various cancers.  <b>SciBX 7(17); doi:10.1038/scibx.2014.501</b> <b>Published online May 1, 2014</b>	Patent and licensing status undisclosed	Tyryshkin, A. <i>et al. Cancer Res.</i> ; published online April 1, 2014; doi:10.1158/0008-5472.CAN-13-1256 <b>Contact:</b> N. Tony Eissa, Baylor College of Medicine, Houston, Texas e-mail: <a href="mailto:teissa@bcm.edu">teissa@bcm.edu</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>Disease models</b>			
Engineered skeletal muscle tissue to model diseased muscle	Engineered skeletal muscle could help identify new muscle-regenerating therapies. Neonatal rat myogenic cells cultured for two weeks resulted in the generation of highly organized muscle bundles composed of laminin-surrounded myofibers encased by fibroblasts, which resembles native muscle. The engineered muscle responded to electrical stimulation and underwent satellite cell-mediated regeneration following muscle injury. In nude mice, implantation of engineered muscles led to vascularization, spontaneous contraction and increased muscle force generation after two weeks post-implantation, whereas implantation of undifferentiated muscle cells led to less integration and function. Next steps include designing a functional human muscle for disease modeling.	Findings unpatented; licensing status not applicable	Juhas, M. <i>et al. Proc. Natl. Acad. Sci. USA</i> ; published online March 31, 2014; doi:10.1073/pnas.1402723111 <b>Contact:</b> Nenad Bursac, Duke University, Durham, N.C. e-mail: <a href="mailto:nbursac@duke.edu">nbursac@duke.edu</a>
<b>SciBX 7(17); doi:10.1038/scibx.2014.502</b> Published online May 1, 2014			
<b>Drug platforms</b>			
Engineered <i>Nicotiana benthamiana</i> to produce glycosylated IgMs	Engineered <i>N. benthamiana</i> could generate glycosylated IgMs to treat human diseases. In engineered <i>N. benthamiana</i> plants lacking plant-specific glycosylation, transfection with vectors encoding IgM components resulted in the production of a therapeutic IgM, PAT-SM6, in high picomolar yields per gram of plant material. The glycosylation pattern of the plant-generated PAT-SM6 was comparable to that of PAT-SM6 produced in a human cell line. In a human lung cancer cell line, the plant- and human cell line-generated forms of PAT-SM6 showed comparable inhibitory action against their target, heat shock 70 kDa protein 5 (glucose-regulated protein, 78 kDa; HSPA5; GRP78). Next steps include using the engineered plants to generate IgMs against antibiotic-refractory bacterial infections. Patrys Ltd. has PAT-SM6, a human mAb that binds HSPA5 and imports low-density lipoprotein into cancer cells, in Phase I/II testing to treat multiple myeloma (MM) and Phase I trials to treat melanoma. Patrys, AstraZeneca plc and Debiopharm Group have PAT-SC1, a human IgM mAb that binds to gastric cancer cells expressing CD55SC-1, in Phase I/II testing to treat gastric cancer and in preclinical development for solid tumors.	Patented; licensing status undisclosed	Loos, A. <i>et al. Proc. Natl. Acad. Sci. USA</i> ; published online March 31, 2014; doi:10.1073/pnas.1320544111 <b>Contact:</b> Herta Steinkellner, University of Natural Resources and Applied Life Sciences, Vienna, Austria e-mail: <a href="mailto:herta.steinkellner@boku.ac.at">herta.steinkellner@boku.ac.at</a>
<b>SciBX 7(17); doi:10.1038/scibx.2014.503</b> Published online May 1, 2014			
<i>Ex vivo</i> wingless-type MMTV integration site family member 7A (WNT7A) treatment of myogenic cells prior to muscle cell transplantation to enhance both fusion with myofibrils and muscle function	Cell culture and mouse studies suggest <i>ex vivo</i> treatment with WNT7A could improve stem cell therapies for muscular dystrophies. In culture, WNT7A increased migration of satellite cell-derived mouse primary myoblasts compared with vehicle or WNT3A. In mice, <i>ex vivo</i> WNT7A increased migration of transplanted primary mouse myoblasts compared with vehicle. In a mouse model of muscular dystrophy, transplantation of human or mouse myogenic cells treated <i>ex vivo</i> with WNT7A improved muscle function and increased their engraftment, dispersal and fusion with myofibrils compared with transplantation of cells treated with WNT3A or vehicle. Next steps could include production of pharmaceutical-grade WNT7A. Fate Therapeutics Inc.'s WNT7A analog FT301 is in preclinical development to treat muscular dystrophy.	Patented; licensed to Fate Therapeutics	Bentzinger, C.F. <i>et al. J. Cell Biol.</i> ; published online April 7, 2014; doi:10.1083/jcb.201310035 <b>Contact:</b> Michael A. Rudnicki, Ottawa Hospital Research Institute, Ottawa, Ontario, Canada e-mail: <a href="mailto:mrudnicki@ohri.ca">mrudnicki@ohri.ca</a>
<b>SciBX 7(17); doi:10.1038/scibx.2014.504</b> Published online May 1, 2014			

## This week in techniques (continued)

Approach	Summary	Licensing status	Publication and contact information
Small molecule modulators of G protein-coupled receptor 183 (GPR183; EB12)	Small molecule modulators of EB12 could be useful for probing the function of the receptor and its relevance to human diseases. EB12 activation stimulates immune cell migration and has been genetically linked to autoimmune diseases including type 1 diabetes, but only one small molecule antagonist has been previously reported and no small molecule agonists have been reported. A chemical screen identified a small molecule agonist of mouse and human EB12 with single-digit micromolar EC <sub>50</sub> values. The agonist was then used to discover two small molecules that antagonized mouse and human EB12 with nanomolar IC <sub>50</sub> values. Next steps include collaborating with academic groups to elucidate the role of the oxysterol and EB12 pathway in human diseases.  <b>SciBX 7(17); doi:10.1038/scibx.2014.505</b> <b>Published online May 1, 2014</b>	Patent and licensing status undisclosed	Gessier, F. <i>et al. J. Med. Chem.</i> ; published online March 28, 2014; doi:10.1021/jm4019355 <b>Contact:</b> Andreas W. Sailer, Novartis Institutes for BioMedical Research, Basel, Switzerland e-mail: <a href="mailto:andreas.sailer@novartis.com">andreas.sailer@novartis.com</a>
<b>Imaging</b>			
Combined use of luminescence imaging and MRI for real-time, <i>in vivo</i> , quantitative monitoring of drug release	A combined strategy using luminescence imaging and MRI could be useful for real-time, quantitative monitoring of drug release <i>in vivo</i> . Nanoparticles designed to release their payload in response to excitation with near-infrared light were loaded with doxorubicin. In a human cancer cell line and in zebrafish treated with the doxorubicin-loaded nanoparticles, the combined imaging strategy using luminescence imaging and MRI enabled real-time monitoring and quantification of doxorubicin release from the nanoparticles. Ongoing work includes using the approach to perform real-time monitoring of drug release in larger animal models, including rabbits and canines.  <b>SciBX 7(17); doi:10.1038/scibx.2014.506</b> <b>Published online May 1, 2014</b>	Unpatented; licensing status not applicable	Liu, J. <i>et al. Angew. Chem. Int. Ed.</i> ; published online March 25, 2014; doi:10.1002/anie.201400900 <b>Contact:</b> Jianlin Shi, Shanghai Institute of Ceramics, Chinese Academy of Sciences, Shanghai, China e-mail: <a href="mailto:jlshi@mail.sic.ac.cn">jlshi@mail.sic.ac.cn</a> <b>Contact:</b> Wenbo Bu, same affiliation as above e-mail: <a href="mailto:wbbu@mail.sic.ac.cn">wbbu@mail.sic.ac.cn</a>
Spectral confocal reflectance microscopy for label-free myelin imaging	Studies in mice and human samples suggest spectral confocal reflectance microscopy could be a label-free method to image myelinated axons. In normal mice, repeated use of spectral confocal reflectance microscopy with multiple wavelengths was able to image myelinated axons at depths of up to 400 μm and track changes in myelination during development. In mice with myelin mutations or treated with a demyelinating agent, the imaging method captured decreases in myelination that matched those captured using fluorescent label-based imaging. In postmortem human brains, the imaging method captured myelinated axons in a manner comparable to fluorescence microscopy. Next steps could include validating the imaging technique in additional models.  <b>SciBX 7(17); doi:10.1038/scibx.2014.507</b> <b>Published online May 1, 2014</b>	Patent and licensing status unavailable	Schain, A.J. <i>et al. Nat. Med.</i> ; published online March 30, 2014; doi:10.1038/nm.3495 <b>Contact:</b> Jaime Grutzendler, Yale School of Medicine, New Haven, Conn. e-mail: <a href="mailto:jaime.grutzendler@yale.edu">jaime.grutzendler@yale.edu</a>
<b>Markers</b>			
Asthma diagnostic based on neutrophil chemotaxis speed	A handheld microfluidic device that measures neutrophil chemotaxis speed could help diagnose asthma. The device separates neutrophils from whole blood and stimulates neutrophil chemotaxis with a chemoattractant. It detected decreased chemotaxis in neutrophils from mildly asthmatic patients compared with neutrophils from nonasthmatics with allergic rhinitis. Using a threshold chemotaxis speed of about 1.55 μm/min, the test accurately diagnosed 22 of 23 patients with asthma and 8 of 11 nonasthmatic controls. Next steps include using the test on broader patient populations with different inflammatory disorders that may affect neutrophil function.  <b>SciBX 7(17); doi:10.1038/scibx.2014.508</b> <b>Published online May 1, 2014</b>	Patent applications filed; licensed by Salus Discovery LLC; available for partnerships to develop improved bioassay solutions	Sackmann, E.K.-H. <i>et al. Proc. Natl. Acad. Sci. USA</i> ; published online April 7, 2014; doi:10.1073/pnas.1324043111 <b>Contact:</b> David J. Beebe, University of Wisconsin-Madison, Madison, Wis. e-mail: <a href="mailto:djbeebe@wisc.edu">djbeebe@wisc.edu</a>

## This week in techniques (continued)

Approach	Summary	Licensing status	Publication and contact information
<i>Solute carrier family 12 potassium-chloride transporter member 2 (SLC12A2; NKCC1)</i> -based markers for schizophrenia	Genetic profiling studies suggest assessing variation in <i>NKCC1</i> expression could help predict schizophrenia risk. <i>NKCC1</i> is expressed as two alternative splice variants— <i>NKCC1a</i> and <i>NKCC1b</i> —and as an ultra-short transcript. Sequencing and analysis of postmortem brain tissue samples showed that schizophrenia patients had lower expression of the <i>NKCC1b</i> and ultra-short transcripts than controls without psychiatric disorders. The rs3087889 SNP in <i>NKCC1</i> was associated with decreased <i>NKCC1b</i> expression and increased risk of schizophrenia. Next steps could include validating the various <i>NKCC1</i> -based markers in larger patient cohorts.	Patent and licensing status unavailable	Morita, Y. <i>et al. J. Neurosci.</i> ; published online April 2, 2014; doi:10.1523/JNEUROSCI.1423-13.2014 <b>Contact:</b> Thomas M. Hyde, Lieber Institute for Brain Development, Baltimore, Md. e-mail: <a href="mailto:thomas.hyde@libd.org">thomas.hyde@libd.org</a>
	<b>SciBX 7(17); doi:10.1038/scibx.2014.509</b> Published online May 1, 2014		



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