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Speed and cost are the potential selling points for nanopore sequencing, but thus far speed has come at the cost of accuracy. Now, a team at UC Santa Cruz has discovered a way to improve the accuracy of nanopore sequencing while retaining its speed, and it has licensed the technology to Oxford Nanopore.

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By Tracey Baas, Senior Editor

Speed and cost are the selling points for nanopore sequencing, which holds the promise of being faster than sequencing technologies currently on the market without needing extensive DNA sample preparation. But thus far speed has come at the cost of accuracy. Now, a team at the **University of California, Santa Cruz** has discovered a way to improve the accuracy of nanopore sequencing while retaining its speed.¹

Oxford Nanopore Technologies Ltd. has licensed the technology and is incorporating it into its nanopore sequencing platforms.

The underlying premise of nanopore sequencing involves pushing a strand of DNA through a pore in a protein or silicon sheet. Because the pore is so small, a coiled nucleic acid molecule will unravel and progress single file through the pore. Each nucleotide produces a distinct signature as it passes through the pore, thus allowing for the sequencing of the nucleic acid chain.

At least five companies are developing nanopore-based devices that can sequence DNA. The companies have not divulged many details about their respective technologies, including the specific pores and what type of surface the pores are embedded in. The companies do have different strategies for pushing the DNA through the pore and for measuring the DNA once it is inside the pore (*see Table 1, “Nanopore sequencing in development”*).

Thus far, a key sticking point has been driving DNA through at a controlled speed that allows for accurate detection of each individual nucleotide's signature. Without any speed controls, DNA will shoot through a nanopore so rapidly that the number of nucleotides cannot be counted.²

To address the problem, the UCSC team combined phi29 DNA polymerase (DNAP) and blocking oligomers to move DNA through a nanopore at a more controlled speed than that which results from relying on just electrophoretic motion induced by an externally applied voltage.

The group previously showed that phi29 DNAP drives DNA strands through a nanopore as the polymerase replicates the DNA. The force of the voltage-induced electric field, acting in the opposite direction of the replication, helps hold the DNA strand taut and reduces its speed through the nanopores.³ The problem was that replication occurred not just at the nanopore, but also in solution, depleting reagents before they reached the nanopore for detection.

To get around that issue, the team turned to blocking oligomers, which protect DNA from polymerase-mediated replication until the DNA-DNAP-blocking oligomer complex reaches the nanopore.

Specifically, the DNA is pulled through the nanopore in one direction by an applied voltage, which leads to unzipping of the blocking oligomer selectively at the pore. The DNA is then driven in the opposite direction



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

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through the nanopore by DNAP-mediated DNA replication. The forward and reverse motion of the DNA through the pore allows for two readouts per nucleotide.

As proof of concept, the group used α -hemolysin nanopores embedded in a lipid bilayer and processed about 500 DNA molecules at 130 molecules per hour per pore. They used an ionic current map to count the number of nucleotides that passed through the pore, but they did not identify the bases.

The researchers opted not to sequence the DNA—instead measuring the accuracy of their approach by counting nucleotides—because the prototype nanopore used, α -hemolysin, does not provide sufficient resolution to read bases. The estimated rate of DNA template error was about 10%–25%.

Results were published in *Nature Biotechnology*.

“It is nice work demonstrating enzymatic motion control of DNA, but it also shows that the field is a long way from having a commercial nanopore sequencing machine,” said Jonathan Rothberg, founder, chairman and CEO of **Ion Torrent Systems Inc.** “I would not at this time say they are sequencing since they did not determine the sequence. Thus far they have only been able to compare signals to what would be expected for the known sequence they used.”

Nevertheless, said Rothberg, the paper “is the most important recent progress in the field. It allows DNA to go through the pore in a way that allows the sequence to be seen.”

“It is nice work demonstrating enzymatic motion control of DNA, but it also shows that the field is a long way from having a commercial nanopore sequencing machine.”

—Jonathan Rothberg,
Ion Torrent Systems Inc.

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Table 1. Nanopore sequencing in development. At least five companies are developing nanopore-based DNA sequencers, which determine base-pair identity by measuring unique signatures generated by each nucleotide as it passes through a pore. Three key design choices distinguish nanopore-based sequencing systems in development: the composition of the nanopore itself, which could be a solid-state material or a biological material consisting of a recombinant channel protein such as a porin; the DNA transport method, which controls how fast nucleotides pass through the pore and is critical to ensure accurate sequencing; and the nature of the signature generated by the DNA as it passes through the pore.

Company	Nanopore composition	DNA transport method	Detection signature	Predicted commercial launch
Genia Technologies Inc.	Biologic	Electronic control moves DNA through nanopores embedded in a lipid bilayer	Ionic current	2013
IBM Research/Arizona Technology Enterprises/Roche (SIX:ROG; OTCQX:RHHBY)/454 Life Sciences Corp.	Solid state	Electronic control moves DNA through nanopores embedded in a silicon chip	Electron tunneling current	Undisclosed
NABsys Inc.	Solid state	Electronic control moves DNA with hybridized oligonucleotide probes through nanopores embedded in a silicon chip ^a	Ionic current	Undisclosed
NobleGen Biosciences Inc.	Solid state	Electronic control moves synthetic DNA template with hybridized oligonucleotide beacons through nanopores in a silicon chip, displacing the beacons ^b	Fluorescence	2014
Oxford Nanopore Technologies Ltd.	Biologic	Processive enzyme moves DNA through nanopores embedded in a lipid bilayer	Ionic current	2H12

^aRequires a preprocessing step in which DNA is hybridized to oligonucleotide probes. ^bRequires a preprocessing step in which DNA is converted into a synthetic DNA template and hybridized to oligonucleotide beacons, which contain a fluorophore and quencher pair. When the beacon is hybridized to the template, fluorescence is quenched and no signal occurs. When the beacon is released from the template, a fluorescence signal occurs.

Ion Torrent is not using nanopore sequencing and instead is developing its benchtop Ion Personal Genome Machine Sequencer and the benchtop Ion Proton Sequencer, which use polymerase-driven DNA replication combined with a proton-based readout to enable the \$1,000 genome. Commercial launch is mid-2012.

The paper “convincingly demonstrates that one of the major challenges of nanopore-based sequencing—movement control of DNA through the nanopore—can be overcome using an enzymatic approach,” said Stefan Roever, CEO of Genia Technologies Inc. “The ability to read the same molecule multiple times, possibly forward and reverse, as demonstrated in the work, is also a significant factor in reducing error rates.”

Genia is developing its Last Gen sequencing platform, which uses biological nanopores embedded in a lipid bilayer with a readout based on ionic current disruption. The company expects commercial availability in 2013.

“I think the work is a nice experimental method showing that DNA motion can be slowed down, but I don’t think the actual experimental design will ever be used in practice for sequencing,” said Charles Cantor, CSO for Sequenom Inc. “The blocking polymers that they used are complementary to the DNA template that they sequenced. This would require one to know the sequence *a priori* to sequencing. Perhaps, as a long shot, the method could be extended to using a panel of generic blocking oligomers, but that would require a whole different set of proof-of-concept experiments.”

“They also use a rather simplistic DNA template so that they avoid problems with secondary structure. I would be interested to see if they could reproduce their findings using longer, more typical DNA sequences,” he told *SciBX*.

The Sequenom Center for Molecular Medicine Inc., a subsidiary of Sequenom Inc., is developing a broad range of diagnostics with a focus on prenatal diseases and conditions, marketed under the name SensiGene.

Implementing the nanopores

Roever did say the paper’s current template register error rate is unusable for a commercial sequencing technique. He thinks accuracy could be improved by including a “readout of an additional signature of any

enzymatic activity—essentially an electric signal indicating the strand has been advanced a single frame—or by reading the signal from several bases in the pore at a time” and then using a deconvolving algorithm to link a specific base with its specific signal.

“Ideally, a combination of both techniques would be used,” he added.

Mark Akeson, chair of biomolecular engineering at UCSC and lead author on the *Nature Biotechnology* paper, told *SciBX*, “The error rate has already been substantially improved and systematized for a working commercial instrument by Oxford Nanopore,” which holds rights to patents covering the technology described in the paper.

An Oxford Nanopore spokesperson said, “We are constantly iterating the system to improve error rates, and we are targeting between 0.1%–2% for our launch product,” adding that the company’s chemistry “is not the published chemistry of our academic partners. Our enzyme and nanopore are undisclosed.”

Regardless of approach, Ion Current’s Rothberg thinks the next big issue for nanopore sequencing companies is fabrication.

“Nanopores, while being miniaturized, have no existing method to be easily fabricated,” he said. “They will be difficult to manufacture and will have significant issues scaling to a practical parallel implementation.”

Baas, T. *SciBX* 5(11); doi:10.1038/scibx.2012.271
Published online March 15, 2012

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Genia Technologies Inc., Mountain View, Calif.
Ion Torrent Systems Inc., San Francisco, Calif.
Oxford Nanopore Technologies Ltd., Oxford, U.K.
Sequenom Center for Molecular Medicine Inc., Grand Rapids, Mich.
Sequenom Inc. (NASDAQ:SQNM), San Diego, Calif.
University of California, Santa Cruz, Calif.

One gap, two approaches

By *Steve Edelson, Executive Editor*

Whereas most academic institutes tackle the translational gap by pushing their assets further along in hopes of attracting an industry partner, Cleveland-based **University Hospitals** is taking the opposite approach by forming a company that will in-license projects. University Hospitals has received a \$50 million gift from the Harrington family and plans to use the money to form the to-be-named company as well as an institute that will act as a feeder for the company by funding projects of physician scientists across the country.

“We’re trying to find a way to support the cadre of physician scientists in academic medicine. These individuals are the most capable of taking scientific inquiry into the clinical realm,” said Jonathan Stamler, director of the newly formed **University Hospitals Harrington Discovery Institute**.

Stamler also is director of the Institute for Transformative Molecular Medicine at **University Hospitals Case Medical Center** and **Case Western Reserve University School of Medicine**.

The UH Harrington Discovery Institute plans to award scholarships to 10 physician scientists this year. The size of the two-year scholarships was not disclosed. The institute plans to form an advisory council in the next few months, after which “we’ll have a national competition that will have a very simple process that asks physician scientists to make a case for something of impact—they have to have identified something that benefits human health,” said Stamler.

In addition to the scholarship dollars, the institute will be able to help physician scientists gain access to resources such as high throughput screening or model systems. “We’ll help give direction that could be in the form of mentoring or it could be money” used to purchase a research service, Stamler told *SciBX*.

For example, the UH Harrington Discovery Institute already has partnered with an undisclosed institution that has a high throughput screening facility.

Stamler said the scholarships will likely be in cancer, cardiovascular disease, infectious disease and neurology.

Inventing the customer

The for-profit company will be able to in-license discoveries supported by the institute’s grants. It also plans to look elsewhere for assets to bring under its roof.

“You really only have two options to cross the translational divide. Everyone is trying to fill it on the academic side by making their academic institutes look more pharma-like and developing their assets further. But no matter what you do on that side, the gap seems to keep getting larger—you can’t fill it in quickly enough and you’re not

resourced to do it and the bar’s getting higher on the company side,” said Stamler. “So we decided to come from the other side as well and create a for-profit company.”

The company has a management team in place, including CEO Bob Keith and CSO David U’Prichard. Keith is the former president and CEO of Catalyst Growth Partners, which provides advisory services for emerging companies. U’Prichard is the former CEO of 3-Dimensional Pharmaceuticals Inc., and before that was chairman of R&D at SmithKline Beecham (now part of **GlaxoSmithKline plc**).

The newco is looking to raise \$100 million. Of that sum, Stamler said the newco already has an anchor investment from UH, other academic institutions in northeast Ohio, multiple Cleveland foundations and high-net worth individuals. He expects the remainder to come from other foundations and institutions across the U.S. as well as from big pharma.

The company will start with 10 projects, and Stamler said the goal is to scale up to “a steady state of 10–12. We hope for IRRs of at least 20%.” Of the projects, Stamler expects one or two will be in-licensing deals from the physician scientist grant program.

Stamler said the newco is similar to venture firms and companies focused on discrete asset-based entities. These include **Atlas Venture**, which formed **Atlas Venture**

Development Corp. to shop for pre-IND and Phase I assets from pharma and spin them into individual structures within a holding entity.¹

Companies like **Amunix Inc.**, **Nimbus Discovery LLC** and **Inception Sciences Inc.** also are conducting drug discovery and spinning out assets into separate entities.

“There are real similarities to project-based financing,” said Stamler. The difference, he said, is the newco will start at an earlier stage of development and will not be spinning out its assets into discrete entities like many of the other asset-focused entities plan to do.

“The company is there to support enduring projects,” typically to about Phase II testing, he said.

Stamler also thinks the newco will have an advantage when it comes to clinical development. “We’re hooked into academic medical centers.”

Edelson, S. *SciBX* 5(11); doi:10.1038/scibx.2012.272

Published online March 15, 2012

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Atlas Venture, Cambridge, Mass.

Atlas Venture Development Corp., Cambridge, Mass.

Case Western Reserve University School of Medicine, Cleveland, Ohio

GlaxoSmithKline plc (LSE:GSK; NYSE:GSK), London, U.K.

Inception Sciences Inc., San Diego, Calif.

Nimbus Discovery LLC, Cambridge, Mass.

University Hospitals, Cleveland, Ohio

University Hospitals Case Medical Center, Cleveland, Ohio

University Hospitals Harrington Discovery Institute, Cleveland, Ohio

Antibodies not needed

By Lev Osherovich, Senior Writer

Italian and American researchers have mouse data showing that the most important function of B cells in fighting some viral infections is not making antibodies but rather stimulating an innate immune response led by macrophages.¹ The findings could point to new vaccine adjuvant strategies for viruses such as rabies and West Nile, assuming the mouse data translate into humans.

A team co-led by Matteo Iannacone and Ulrich von Andrian made the discovery while studying the early steps in the immune response to vesicular stomatitis virus (VSV), a veterinary pathogen that serves as a model for neurotropic viruses.

Iannacone is group leader in the division of immunology at the **San Raffaele Scientific Institute**. Von Andrian is professor of immunopathology at **Harvard Medical School**.

Iannacone said the researchers were trying to understand the precise sequence of immunological events in VSV infections, in which the virus gravitates to the CNS if unchecked by a combination of innate and adaptive immune responses in the lymph nodes.

In a previous study the team showed a successful immune response against VSV required macrophages, a type of innate immune cell.² Ordinarily, macrophages in the lymph nodes ingest viral particles, deliberately become infected by the virus and then launch the type I interferon (IFN) response that turns on other immune cells and helps neurons ward off the infection.

“In our previous paper, we showed that the macrophages in the lymph nodes capture the virus,” said von Andrian. “We depleted those macrophages and infected the mice, which caused the mice to die from CNS penetration of the virus.”

Von Andrian noted that a particularly intriguing finding from the paper was that macrophage-deficient mice often had high titers of antibodies against VSV but died nonetheless. Based on this, the team suspected that “making the antibodies is not sufficient for protection,” said von Andrian. “We thus asked whether the antibodies were even necessary.”

Ain't got no (anti)body

Von Andrian and Iannacone began their new study by confirming prior observations by other researchers that mice engineered to lack B cells succumbed to VSV infection while similarly treated wild-type controls survived.

The surprise came when the team repeated the experiment using a mouse strain engineered with B cells that were unable to splice antibody genes but were otherwise functional. Those mice proved as resistant to VSV as wild-type controls despite having no detectable antibodies.

VSV-infected mice with antibody-deficient B cells had levels of lymph node macrophage activation and type I IFN response similar to those in wild-type controls.

“We found that it wasn't the antibodies that were needed,” said Iannacone.

The next step was finding out what the B cells were making that was really needed to combat the virus. The researchers suspected the key was lymphotoxins, a family of cytokines that promote macrophage proliferation in lymph nodes.

Indeed, mice treated with a decoy receptor that binds and inactivates lymphotoxin- α (Lta) and Ltb (p33) had lower macrophage activation and type I IFN response than untreated controls and succumbed to VSV infection.

Altogether, the findings suggest uptake and infection of macrophages by VSV is an essential step in launching an innate immune response against the virus. B cells help this process by secreting lymphotoxins, which help the macrophages take up and replicate the virus, resulting in a protective type I IFN response.

Results were reported in *Immunity* and were not patented.

Adjuvant opportunity

Von Andrian and Iannacone's findings challenge the notion that B cells are purely antibody factories. The key question is whether, as in mice, the human immune system uses B cell-derived lymphotoxins to increase antiviral immunity.

“This paper shows that there is a non-antibody-mediated effector mechanism” for B cells, said Patrick Iversen, SVP of research and innovation at **AVI BioPharma Inc.** “The vaccine world may now understand that antibodies aren't the only important thing.”

AVI has antiviral oligonucleotides in Phase I testing for Ebola virus and Marburg virus.

“This is somewhat of a novel finding,” said Jim Tartaglia, VP and new vaccine project head in North America at **Sanofi's** Sanofi Pasteur vaccine division. “The results are intriguing and worth following up to understand the relevance in other viruses and human pathogens.”

Tartaglia cautioned that many features of the mouse and human immune systems differ, so it will be necessary to replicate the findings in cell culture or mouse models of human viral infection.

Iannacone and von Andrian agreed but said first efforts are to repeat the VSV experiments in mice with humanized immune systems.

Iannacone suspects lymphotoxins could be used to improve immunity to human viruses that resemble VSV, such as rabies virus or West Nile virus. He noted that although “there is a vaccine for rabies that works beautifully,” timely delivery of that therapy—a combination of neutralizing antibodies and a prophylactic vaccine—is a challenge.

“VSV doesn't infect humans, but it's in the same family as rabies, so we think [these findings] could apply to rabies,” said Iannacone. “This study might suggest that passive prophylaxis for rabies could be boosted with lymphotoxins.”

Von Andrian wants to determine whether lymphotoxins also contribute to the immune response to influenza or HIV, which do not infect the

(Continues on p. 6)

“VSV doesn't infect humans, but it's in the same family as rabies, so we think [these findings] could apply to rabies. This study might suggest that passive prophylaxis for rabies could be boosted with lymphotoxins.”

—**Matteo Iannacone,**
San Raffaele Scientific Institute

Halofuginone target ID

By Joanne Kotz, Senior Editor

A U.S. and South Korean research team has identified the molecular target of halofuginone, a small molecule antifibrotic and anti-inflammatory compound.¹ The findings could help guide the design of next-generation halofuginone analogs with improved pharmacological profiles and may help determine the specific indications most amenable to treatment with the analogs.

Halofuginone is a halogenated derivative of the plant alkaloid febrifugine, which is found in hydrangea roots. In preclinical animal models, halofuginone prevents fibrosis by decreasing fibroblast-mediated production of extracellular matrix proteins such as collagen and lowers inflammation by blocking the differentiation of autoimmune-mediating T helper type 17 (Th17) cells.

However, clinical development of halofuginone has been stymied by the molecule's poor drug-like properties and GI toxicity.

"Halofuginone is an interesting molecule in the context of fibrosis research, as it is one of only a few small molecule compounds identified early on in the field that could inhibit fibroblast production of collagen. Ironically, we did not know the specific molecular target for any of these early compounds when they were identified. Although relatively potent in cell-based assays, halofuginone's poor oral bioavailability, questionable tolerance profile and limited patent life prevented it from being developed successfully," said Mark Lupher Jr., CSO at fibrosis company **Promedior Inc.**

"A new understanding of its specific molecular target, however, could show promise in enabling the identification of new chemical classes with superior pharmacologic profiles to the canonical halofuginone."

—Mark Lupher, Promedior Inc.

"A new understanding of its specific molecular target, however, could show promise in enabling the identification of new chemical classes with superior pharmacologic profiles to the canonical halofuginone," Lupher said. "If a potent, safe and bioavailable analog could be identified, it would have potential in a large number of fibrotic and inflammatory indications."

A team led by Malcolm Whitman, Tracy Keller, Ralph Mazitschek and Chang-Yeol Yeo set out to identify halofuginone's target.

Whitman is a professor of developmental biology and Keller is an instructor in developmental biology at the **Harvard School of Dental Medicine**. Mazitschek is an assistant professor in the radiology department at **Harvard Medical School** and co-director of the chemical biology platform in the Center for Systems Biology at **Massachusetts General Hospital**. Yeo is an assistant professor in the division of life and pharmaceutical sciences at **Ewha Womans University**.

The researchers had a good starting point. In 2009, they reported in *Science* in collaboration with Anjana Rao that halofuginone induced the amino acid response pathway in fibroblasts and Th17 cells,² the two cell types through which halofuginone exerts its effects.

Rao is a professor at the **La Jolla Institute for Allergy & Immunology**.

The amino acid response pathway is triggered by nutritional stress that results from low levels of amino acids and leads to decreased levels of protein synthesis as a way to conserve nutrients and improve cellular survival.

Now, the researchers have probed the protein synthesis pathway to look for components that are altered or impaired in the presence of halofuginone.

An *in vitro* protein translation assay showed that halofuginone inhibited translation of a reporter gene only if the resulting protein

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(Continued from "Antibodies not needed," p. 5)

CNS but do infect macrophages. For those viruses, it's unclear whether macrophage infection ultimately helps or harms the immune response.

Tartaglia thinks the lymphotoxin mechanism described by von Andrian and Iannacone may be relevant to other viral infections but wants to see more data.

"I see this [mechanism] as being potentially useful for broader vaccine development, but I couldn't say right now for which vaccines because I'd like to see it replicated in human immune cells," said Tartaglia.

One concern about using lymphotoxins as adjuvants is the proteins' proinflammatory effects. For example, treating patients with lymphotoxins runs the risk of triggering autoimmunity. If so, further study of the downstream pathways activated by lymphotoxins could help identify ways to separate the antiviral and autoimmune effects.

Rather than using lymphotoxins themselves, Tartaglia said that it may "make sense to develop small molecules that trigger desirable antiviral effects as part of an adjuvant formulation or to engineer an

immunogen that triggers these mechanisms" without eliciting full-blown autoimmunity.

Osheroich, L. *SciBX* 5(11); doi:10.1038/scibx.2012.273

Published online March 15, 2012

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COMPANIES AND INSTITUTIONS MENTIONED

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Harvard Medical School, Boston, Mass.
Sanofi (Euronext:SAN; NYSE:SNY), Paris, France
San Raffaele Scientific Institute, Milan, Italy

contained proline residues. That result suggested halofuginone inhibited the prolyl-tRNA synthetase domain of glutamyl-prolyl-tRNA synthetase (EPRS), a dual-function tRNA that binds glutamate and proline residues and incorporates them into proteins. Indeed, halofuginone inhibited the prolyl-tRNA synthetase domain of EPRS with a K_i of 18 nM *in vitro*.

In cell culture, both the antifibrotic and anti-inflammatory effects of halofuginone were reversed by the addition of proline.

Collectively, the results confirm that EPRS is halofuginone's target. Results were published in *Nature Chemical Biology*.

Building a better inhibitor

Shelia Violette, VP of research at **Stromedix Inc.**, said it should now be possible to determine whether halofuginone's GI toxicity is due to effects on the amino acid response pathway or off-target effects.

Stromedix's STX-100, a humanized mAb against integrin $\alpha_v\beta_6$, will be tested in a Phase II trial to treat idiopathic pulmonary fibrosis (IPF) to be initiated later this year. In February, **Biogen Idec Inc.** announced it was acquiring Stromedix.

"If the data remain strong and indicate that the beneficial effects of halofuginone are related to activation of the amino acid response pathway and that toxicity can be dissected away, then one could build a series of chemical compounds around this target that have attractive drug properties, such as oral bioavailability, stability, half-life and pharmacokinetics," said Violette.

Indeed, Whitman said the team now plans to do just that, using proline rescue to investigate whether the molecule's toxicity is on target or off target.

Lupher said the identification of EPRS as halofuginone's target will enable two previously unavailable approaches for identifying new chemical classes of EPRS inhibitors. One option is *in vitro* high throughput screening assays using the purified prolyl-tRNA synthetase domain of EPRS. The other is obtaining a crystal structure of halofuginone bound to EPRS to facilitate structure-based drug design.

"We're now thinking of how to distribute the drug better *in vivo*," Whitman said.

Mazitschek told *SciBX* the team already has identified halofuginone derivatives that retain activity and have better solubility and stability in solution.

The researchers are using these derivatives as a starting point for building prodrugs that are activated systemically to overcome GI toxicity. Finally, the team is developing topically active compounds that limit systemic exposure.

Mazitschek is a cofounder of **Shape Pharmaceuticals Inc.**, which has a topical histone deacetylase (HDAC) inhibitor in Phase I testing for cutaneous T cell lymphoma (CTCL).

Probing the pathway

Knowing halofuginone's target also will help investigations of the amino acid response pathway and its role in disease.

"The identification of a molecular target of halofuginone opens the door to asking more specifically how activation of the amino acid

response pathway relates to the occurrence and progression of various human diseases. This information could help fine-tune the disease indications that might be affected by impacting this pathway," said Violette.

"There wasn't a good tool compound for the amino acid response, so it's been difficult to interrogate this highly conserved pathway," said Mazitschek. The team is now looking at the effects of perturbing the amino acid response pathway in rheumatoid arthritis (RA) and other preclinical models of fibrotic and inflammatory diseases, Whitman added.

Whitman said the team is also collaborating with an undisclosed company looking for druggable targets further downstream in the pathway.

At least one company has a halofuginone analog about to enter the clinic. By year end, **Halo Therapeutics LLC** plans to start Phase II testing of its HT-100 to treat Duchenne muscular dystrophy (DMD), in which muscle fibrosis occurs during disease progression.³ The company said its compound lacks the GI issues of the parent molecule. Halo declined to discuss whether the paper has implications for HT-100's development.

The researchers have filed patent applications covering therapeutic uses of tRNA synthetase inhibitors in inflammatory and fibrotic indications and covering composition of matter of the new halofuginone derivatives. The IP is available for licensing through the **Harvard University Office of Technology Development**.

Kotz, J. *SciBX* 5(11); doi:10.1038/scibx.2012.274
Published online March 15, 2012

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e-mail: cyeo@ewha.ac.kr
2. Sundrud, M.S. *et al. Science* **324**, 1334–1338 (2009)
3. Fisher, A. *BioCentury* **20**(7), A7; Feb. 13, 2012

COMPANIES AND INSTITUTIONS MENTIONED

Biogen Idec Inc. (NASDAQ:BIIB), Weston, Mass.
Ewha Womans University, Seoul, South Korea
Halo Therapeutics LLC, Newton, Mass.
Harvard Medical School, Boston, Mass.
Harvard School of Dental Medicine, Boston, Mass.
Harvard University Office of Technology Development, Cambridge, Mass.
La Jolla Institute for Allergy & Immunology, La Jolla, Calif.
Massachusetts General Hospital, Boston, Mass.
Promedior Inc., Malvern, Pa.
Shape Pharmaceuticals Inc., Cambridge, Mass.
Stromedix Inc., Cambridge, Mass.

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
Autoimmune disease				
Multiple sclerosis (MS)	CC chemokine receptor 4 (CCR4; CD194)	<p>Mouse studies suggest inhibiting CCR4 on dendritic cells could help treat MS. In mice with experimental autoimmune encephalomyelitis (EAE), <i>Ccr4</i> knockout decreased disease severity and immune cell infiltration into the spinal cord compared with wild-type <i>Ccr4</i> expression. In the EAE model, <i>Ccr4</i> knockout mice that received intracerebral delivery of <i>Ccr4</i>^{+/+} dendritic cells developed encephalomyelitis. Next steps could include developing inhibitors of CCR4 on dendritic cells. Kyowa Hakko Kirin Co. Ltd.'s mogamulizumab, a humanized mAb against CCR4, is under review to treat T cell lymphoma. Affitech A/S's CCR4 mAb, AT008, is in preclinical testing for cancer, autoimmune and inflammatory indications.</p> <p>SciBX 5(11); doi:10.1038/scibx.2012.275 Published online March 15, 2012</p>	Findings unpatented; unavailable for licensing	<p>Poppensieker, K. <i>et al. Proc. Natl. Acad. Sci. USA</i>; published online Feb. 21, 2012; doi:10.1073/pnas.1114153109 Contact: Judith Alferink, University of Bonn, Bonn, Germany e-mail: judith.alferink@ukb.uni-bonn.de</p>
Multiple sclerosis (MS)	Phosphodiesterase-7 (PDE-7)	<p><i>In vitro</i> and mouse studies identified furan-derived compounds that could help treat MS. <i>In vitro</i>, a lead compound inhibited PDE-7 with a single-digit micromolar IC₅₀ value. In a mouse model of experimental autoimmune encephalomyelitis (EAE), the compound delayed the development of motor disability and decreased weight loss compared with vehicle. Next steps include developing and testing more efficacious PDE-7 inhibitors. BRAINco Biopharma S.L. has PDE-7 inhibitors in preclinical development to treat MS.</p> <p>SciBX 5(11); doi:10.1038/scibx.2012.276 Published online March 15, 2012</p>	Patent application filed; licensed to BRAINco Biopharma	<p>Redondo, M. <i>et al. J. Med. Chem.</i>; published online March 5, 2012; doi:10.1021/jm201720d Contact: Carmen Gil, Institute of Medical Chemistry, Madrid, Spain e-mail: cgil@iqm.csic.es</p>
Cancer				
Breast cancer	RAR-related orphan receptor A (RORA); semaphorin 3F (SEMA3F)	<p>Mouse and patient sample studies suggest increasing RORA signaling through SEMA3F could treat breast cancer. In a mouse xenograft model of breast cancer, induction of RORA expression delayed tumor growth and led to the formation of smaller tumors compared with what was seen using vector control. In a cultured human breast cancer cell line expressing RORA, small interfering RNA against SEMA3F restored tumor cell invasiveness compared with control siRNA. In a panel of 259 patient samples, low expression of RORA and SEMA3F was associated with disease progression and reduced survival. Next steps include evaluating the function of RORA and SEMA3F in a transgenic mouse model of cancer.</p> <p>SciBX 5(11); doi:10.1038/scibx.2012.277 Published online March 15, 2012</p>	Unpatented; unavailable for licensing	<p>Xiong, G. <i>et al. Cancer Res.</i>; published online Feb. 20, 2012; doi:10.1158/0008-5472.CAN-11-2762 Contact: Ren Xu, University of Kentucky, Lexington, Ky. e-mail: ren.xu2010@uky.edu</p>

This week in therapeutics

Indication	Target/marker/pathway	Summary	Licensing status	Publication and contact information
Cancer	Not applicable	<i>In vitro</i> and mouse studies showed antiangiogenic compounds had the undesirable side effect of increasing proliferation of cancer stem cells (CSCs), suggesting antiangiogenic compounds should be combined with CSC-targeting molecules. In mice with human breast cancer xenografts, the antiangiogenic small molecule Sutent sunitinib caused primary tumor regression but increased the number of CSCs, tumor hypoxia and tumor invasiveness compared with vehicle. Next steps include testing antiangiogenic compounds and CSC-targeted therapies in preclinical cancer models. Pfizer Inc. markets the receptor tyrosine kinase (RTK) inhibitor Sutent to treat various cancers.	Patent and licensing status unavailable	Conley, S.J. <i>et al. Proc. Natl. Acad. Sci. USA</i> ; published online Jan. 23, 2012; doi:10.1073/pnas.1018866109 Contact: Max S. Wicha, University of Michigan, Ann Arbor, Mich. e-mail: mwicha@umich.edu
		SciBX 5(11); doi:10.1038/scibx.2012.278 Published online March 15, 2012		
Multiple myeloma (MM)	Glycogen synthase kinase 3 β (GSK3B); NF- κ B; nuclear factor of κ light polypeptide gene enhancer in B cells 2 p49/p100 (NFKB2; p52)	<i>In vitro</i> and mouse studies suggest inhibiting GSK3B could help treat a subset of MM with constitutively active NF- κ B signaling. In mice with an MM cell line that had an activated NF- κ B pathway, transplantation of cells expressing a mutant form of the NF- κ B-inhibitory protein NFKB2 decreased tumor growth compared with transplantation of cells expressing wild-type NFKB2. In the MM cell line, inhibitors of GSK3B, which phosphorylates NFKB2, decreased both NF- κ B signaling and cell viability compared with vehicle. Next steps include testing GSK3B inhibitors in animal models of MM. DiaMedica Inc.'s GSK3B inhibitor DM-99 is in Phase II testing to treat diabetes. Neurim Pharmaceuticals Ltd.'s Neu-120, a GSK3B inhibitor, is in Phase II testing to treat Parkinson's disease (PD).	Unpatented; an anti-phospho-NFKB2 antibody that can measure the efficacy of GSK3B inhibition is available for licensing	Busino, L. <i>et al. Nat. Cell Biol.</i> ; published online March 4, 2012; doi:10.1038/ncb2463 Contact: Michele Pagano, NYU Cancer Institute, New York University Langone Medical Center, New York, N.Y. e-mail: michele.pagano@nyumc.org
		SciBX 5(11); doi:10.1038/scibx.2012.279 Published online March 15, 2012		
Endocrine/metabolic disease				
Diabetes; obesity	Acetyl-coenzyme A carboxylase- β (ACACB; ACC2)	Mouse studies suggest inhibiting ACC2 could help treat or prevent metabolic diseases. In mice fed a high-fat and high-cholesterol diet, <i>Acc2</i> knockout decreased serum glucose and triglyceride levels, fat pad size and total body weight compared with wild-type <i>Acc2</i> expression. <i>Acc2</i> knockout mice fed a normal or high-fat diet had greater lipogenic enzyme expression than wild-type controls fed the same diet, suggesting that inhibiting <i>Acc2</i> could protect against metabolic syndrome despite increasing lipogenesis. Next steps include developing an ACC2 inhibitor that can completely block enzyme activity. Accera Inc.'s AC-8632, a nonselective ACC2 inhibitor, is in preclinical testing to treat Parkinson's disease (PD).	Patent status not applicable; unavailable for licensing	Abu-Elheiga, L. <i>et al. J. Biol. Chem.</i> ; published online Feb. 23, 2012; doi:10.1074/jbc.M111.309559 Contact: Salih J. Wakil, Baylor College of Medicine, Houston, Texas e-mail: swakil@bcm.edu
		SciBX 5(11); doi:10.1038/scibx.2012.280 Published online March 15, 2012		

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Indication	Target/marker/pathway	Summary	Licensing status	Publication and contact information
Diabetes; obesity	Cannabinoid CB ₁ receptor (CNR1)	<p><i>In vitro</i> and rodent studies identified peripherally restricted CNR1 antagonists that could help treat metabolic diseases. <i>In vitro</i>, the lead compounds inhibited CNR1 with nanomolar potency. In rats, oral dosing of the compounds led to low ng/mL concentrations in serum and undetectable levels in the brain. Next steps include <i>in vivo</i> studies with the compounds in disease models.</p> <p>TM38837, a peripherally restricted CNR1 antagonist from 7TM Pharma A/S, is in Phase I testing to treat diabetes and obesity.</p> <p>Jenrin Discovery Inc.'s peripherally restricted CNR1 antagonist, JD-2114, is in preclinical testing for diabetes and liver disease.</p> <p>SciBX 5(11); doi:10.1038/scibx.2012.281 Published online March 15, 2012</p>	Patent applications filed; available for licensing	<p>Fulp, A. <i>et al. J. Med. Chem.</i>; published online Feb. 28, 2012; doi:10.1021/jm201731z</p> <p>Contact: Rangan Maitra, RTI International, Research Triangle Park, N.C. e-mail: rmaitra@rti.org</p>
Infectious disease				
Viral infection	Lymphotoxin- α (LTA); LTB (p33)	<p>Mouse studies suggest lymphotoxin could be used to stimulate the innate immune response against neurotropic viruses. In a mouse model of viral infection, <i>Ltb</i> knockout mice or mice treated with a decoy receptor that blocks Lta and Ltb signaling had lower macrophage activation, antiviral response and survival than wild-type or mock-treated controls, respectively. Next steps include testing the effect of lymphotoxin-mediated macrophage activation on infection with human neurotropic viruses including rabies virus, West Nile virus and herpes simplex virus (<i>see Antibodies not needed</i>, page 5).</p> <p>SciBX 5(11); doi:10.1038/scibx.2012.282 Published online March 15, 2012</p>	Unpatented; licensing status not applicable	<p>Moseman, E.A. <i>et al. Immunity</i>; published online March 1, 2012; doi:10.1016/j.immuni.2012.01.013</p> <p>Contact: Ulrich H. von Andrian, Harvard Medical School, Boston, Mass. e-mail: uva@hms.harvard.edu</p> <p>Contact: Matteo Iannacone, San Raffaele Scientific Institute, Milan, Italy e-mail: matteo.iannacone@hsr.it</p>
Inflammation				
Asthma	Integrin $\alpha_v\beta_8$	<p>Studies in mice suggest inhibiting integrin $\alpha_v\beta_8$ could help treat asthma. In a mouse model of allergen-induced asthma, dendritic cell-specific deletion of integrin $\alpha_v\beta_8$ decreased airway hyper-responsiveness and the development of T helper type 17 (Th17) cells compared with integrin $\alpha_v\beta_8$ expression. The depletion did not lower the number of $\gamma\delta$ T cells, which are involved in pulmonary defense against pathogens. Next steps include developing specific inhibitors of integrin $\alpha_v\beta_8$.</p> <p>SciBX 5(11); doi:10.1038/scibx.2012.283 Published online March 15, 2012</p>	Patent and licensing status undisclosed	<p>Kudo, M. <i>et al. Nat. Med.</i>; published online March 4, 2012; doi:10.1038/nm.2684</p> <p>Contact: Dean Sheppard, University of California, San Francisco, Calif. e-mail: dean.sheppard@ucsf.edu</p>
Neurology				
Alzheimer's disease (AD)	Not applicable	<p>Studies in mice suggest compounds from <i>Withania somnifera</i> could help treat AD. In a mouse model of AD, orally administered <i>W. somnifera</i> extract increased liver clearance of β-amyloid (Aβ), decreased levels of Aβ in the brain and improved cognitive function compared with vehicle. Next steps include isolating specific compounds responsible for the observed effects and performing preclinical toxicology studies.</p> <p>SciBX 5(11); doi:10.1038/scibx.2012.284 Published online March 15, 2012</p>	Patent pending; available for licensing	<p>Sehgal, N. <i>et al. Proc. Natl. Acad. Sci. USA</i>; published online Jan. 30, 2012; doi:10.1073/pnas.1112209109</p> <p>Contact: Vijayalakshmi Ravindranath, National Brain Research Centre, Haryana, India e-mail: viji@cns.iisc.ernet.in</p>

This week in therapeutics

Indication	Target/marker/pathway	Summary	Licensing status	Publication and contact information
Cognitive dysfunction	AMPA 1 glutamate receptor (GRIA1; GLUR1); NMDA receptor NR1 subtype (GRIN1; NR1); proteasome	Rat studies suggest blocking glutamate receptor degradation could help prevent stress-induced cognitive impairment. In rats, repeated stress led to degradation of Gria1 and Nr1 via the ubiquitin-proteasome pathway and deficits in prefrontal cortex-mediated cognitive processes compared with no stress. In the stressed rats, a proteasome inhibitor prevented the loss of glutamatergic signaling and associated cognitive impairment compared with saline. Next steps include developing and evaluating brain-penetrant compounds targeting components of the pathway, including glutamate receptors. SciBX 5(11); doi:10.1038/scibx.2012.285 Published online March 15, 2012	Unpatented; licensing status not applicable	Yuen, E.Y. <i>et al. Neuron</i> ; published online March 8, 2012; doi:10.1016/j.neuron.2011.12.033 Contact: Zhen Yan, State University of New York at Buffalo, Buffalo, N.Y. e-mail: zhenyan@buffalo.edu
Neurology	CXC chemokine receptor 6 (CXCR6); chemokine CXC motif ligand 16 (CXCL16)	Cell culture studies suggest agonizing CXCR6 could help prevent neuronal cell death. In cultured hippocampal neurons, addition of CXCL16 decreased glutamate-induced cell death compared with vehicle addition. The effect was dependent on expression of the CXCL16 receptor, CXCR6. Next steps could include screening for CXCR6 agonists and testing CXCL16 in mouse models of neurological diseases. SciBX 5(11); doi:10.1038/scibx.2012.286 Published online March 15, 2012	Patent application filed; licensing status undisclosed	Rosito, M. <i>et al. J. Neurosci.</i> ; published online Feb. 29, 2012; doi:10.1523/JNEUROSCI.4046-11.2012 Contact: Flavia Trettel, Sapienza University of Rome, Italy e-mail: flavia.trettel@uniroma1.it
Spinal cord injury (SCI)	Purinergic receptor P2X ligand-gated ion channel 4 (P2RX4; P2X4)	Mouse studies suggest inhibiting P2X4 could help improve recovery following SCI. In a mouse model of SCI, P2x4 levels were greater in spinal cord neurons than in control neurons. In the mouse model, P2x4 knockout decreased lesion size and microglia and macrophage infiltration into the spinal cord, and increased functional recovery compared with wild-type P2x4 expression. Next steps could include developing P2X4 inhibitors. SciBX 5(11); doi:10.1038/scibx.2012.287 Published online March 15, 2012	Patent and licensing status unavailable	de Rivero Vaccari, J.P. <i>et al. J. Neurosci.</i> ; published online Feb. 29, 2012; doi:10.1523/JNEUROSCI.4930-11.2012 Contact: Steve Lacroix, Center Hospital of the Laval University Research Center, Quebec City, Quebec, Canada e-mail: steve.lacroix@crchul.ulaval.ca
Various				
Infectious disease; inflammation	IL-22	Mouse studies suggest IL-22 could help improve thymic recovery following infection or immunodepletion. Thymic recovery following total body irradiation was impaired in <i>Il-22</i> -deficient mice compared with that in either <i>Il-22</i> -deficient mice treated with recombinant <i>Il-22</i> or wild-type mice. In the <i>Il-22</i> -deficient mice, recombinant <i>Il-22</i> increased thymic recovery synergistically with hematopoietic stem cell transplant (HSCT) compared with saline control. Next steps include studying the impact of <i>Il-22</i> on immune recovery following HSCT. SciBX 5(11); doi:10.1038/scibx.2012.288 Published online March 15, 2012	Patent application filed for use of IL-22 as a thymopoietic growth factor; available for licensing	Dudakov, J.A. <i>et al. Science</i> ; published online March 1, 2012; doi:10.1126/science.1218004 Contact: Jarrod A. Dudakov, Memorial Sloan-Kettering Cancer Center, New York, N.Y. e-mail: dudakovj@mskcc.org Contact: Marcel R.M. van den Brink, same affiliation as above e-mail: vandenbm@mskcc.org

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
Assays & screens			
<i>Ex vivo</i> microfluidic measurement of blood conductance to determine disease severity in patients with sickle cell disease	<p>A microfluidic device that simulates vaso-occlusive events could help determine disease severity in patients with sickle cell disease, monitor disease progression and guide treatment. The device ran blood samples through multiple deoxygenation-reoxygenation cycles and measured the resulting rate of decrease in blood conductance. In samples from 29 patients with sickle cell disease, the rate of decrease in blood conductance directly correlated with disease severity. In blood samples from patients with severe disease, the addition of 5-hydroxymethyl-2-furfural lowered the rate of blood conductance decreases compared with no treatment. Future studies could include validating the findings in a prospective trial in a larger patient population or in individual patients followed longitudinally.</p> <p>5-hydroxymethyl-2-furfural (Aes-103), an aromatic aldehyde that increases the affinity of sickle hemoglobin for oxygen from AesRx LLC, is in Phase I testing to treat sickle cell disease.</p> <p>SciBX 5(11); doi:10.1038/scibx.2012.289 Published online March 15, 2012</p>	Patent and licensing status unavailable	<p>Wood, D.K. <i>et al. Sci. Transl. Med.</i>; published online Feb. 29, 2012; doi:10.1126/scitranslmed.3002738 Contact: L. Mahadevan, Harvard University, Cambridge, Mass. e-mail: lm@seas.harvard.edu Contact: John M. Higgins, same affiliation as above e-mail: john_higgins@hms.harvard.edu</p>
High throughput sequencing platform for small molecule cancer drug discovery	<p>A high throughput sequencing platform could help discover small molecule cancer therapeutics. The platform quantifies gene expression using an RNA annealing, selection, ligation and sequencing strategy that was designed to profile mRNA isoforms. As proof of concept, the method was used to identify a series of small molecules that blocked androgen-induced gene expression in a human prostate cancer cell line. One of the top hits, the cardiac glycoside peruvoside, inhibited growth with an IC₅₀ value of 50 nM. Next steps include working with industry partners to test the platform.</p> <p>SciBX 5(11); doi:10.1038/scibx.2012.290 Published online March 15, 2012</p>	Patented; licensed to 255xpress Inc.	<p>Li, H. <i>et al. Proc. Natl. Acad. Sci. USA</i>; published online March 6, 2012; doi:10.1073/pnas.1200305109 Contact: Xiang-Dong Fu, University of California, San Diego, La Jolla, Calif. e-mail: xdfu@ucsd.edu Contact: Sheng Ding, Gladstone Institute of Cardiovascular Disease, San Francisco, Calif. e-mail: sheng.ding@gladstone.ucsf.edu Contact: Michael G. Rosenfeld, University of California, San Diego, La Jolla, Calif. e-mail: mrosenfeld@ucsd.edu</p>
Probes for measuring the activity of multiple cancer-associated kinases in tissue lysates	<p>Probes that can measure the activity of multiple kinases in tissue lysates could be used to identify new biomarkers and guide treatment in cancer. In matched tumor and healthy tissue samples from cancer patients, a panel of substrates was identified that fluoresced when phosphorylated by five different cancer-associated kinases known to be activated in breast, prostate and lung cancers. Next steps could include expanding the panel to incorporate probes of additional kinases and identifying previously unknown kinases that are activated in different types of cancer.</p> <p>SciBX 5(11); doi:10.1038/scibx.2012.291 Published online March 15, 2012</p>	Patent and licensing status unavailable	<p>Stains, C.I. <i>et al. Chem. Biol.</i>; published online Feb. 24, 2012; doi:10.1016/j.chembiol.2011.11.012 Contact: Barbara Imperiali, Massachusetts Institute of Technology, Cambridge, Mass. e-mail: imper@mit.edu</p>

This week in techniques

Approach	Summary	Licensing status	Publication and contact information
Single-cell, whole-genome sequencing of patient tumor samples	<p>A protocol for whole-genome, single-cell sequencing could help identify new cancer markers and therapeutic targets. Individual cells were isolated from kidney cancer samples from patients, and the samples' DNA was amplified. Exome sequencing of the amplified DNA identified genetic variability at the single-cell level as well as mutational heterogeneity in several genes that play a role in disease progression. Next steps include additional sequencing studies in diverse tumor types.</p> <p>SciBX 5(11); doi:10.1038/scibx.2012.292 Published online March 15, 2012</p>	Patent applications filed for findings in both studies; licensing status undisclosed; available for collaboration	<p>Hou, Y. <i>et al. Cell</i>; published online March 2, 2012; doi:10.1016/j.cell.2012.02.028 Contact: Jun Wang, BGI-Shenzhen, Shenzhen, China e-mail: wangj@genomics.org.cn Contact: Yingrui Li, same affiliation as above e-mail: liyr@genomics.org.cn Contact: Xiuqing Zhang, same affiliation as above e-mail: zhangxq@genomics.org.cn</p> <p>Xu, X. <i>et al. Cell</i>; published online March 1, 2012; doi:10.1016/j.cell.2012.02.025 Contact: Jun Wang, BGI-Shenzhen, Shenzhen, China e-mail: wangj@genomics.org.cn Contact: Yingrui Li, same affiliation as above e-mail: liyr@genomics.org.cn Contact: Michael Dean, National Institutes of Health, Bethesda, Md. e-mail: deanm@mail.nih.gov</p>
Chemistry			
Catalyst-based, site-selective oxidation of methyl carbons in hydroxy- γ -methyl or keto- γ -methyl structures for natural product synthesis	<p>A catalyst specific for an oxygen-methyl structure could help streamline the synthesis of therapeutic saponins and other natural products. In molecules containing a hydroxy-γ-methyl or keto-γ-methyl structure, the catalyst selectively oxidized the methyl carbon to an alcohol to yield new derivatives of the antitumor and antiviral agent oleanolic acid and other saponin and terpenoid structures. Future studies could include optimizing the reaction to increase yields.</p> <p>SciBX 5(11); doi:10.1038/scibx.2012.293 Published online March 15, 2012</p>	Patent and licensing status unavailable	<p>Simmons, E.M. & Hartwig, J.F. <i>Nature</i>; published online Feb. 29, 2012; doi:10.1038/nature10785 Contact: John F. Hartwig, University of California, Berkeley, Calif. e-mail: jhartwig@berkeley.edu</p>
Disease models			
Mouse model of corticosterone-induced post-traumatic stress disorder (PTSD)	<p>A mouse model of corticosterone-induced PTSD could guide the development of new therapies for the disorder. In mice undergoing fear conditioning, infusions of the stress hormone corticosterone into the hippocampus induced PTSD-like memory impairments compared with infusion of artificial cerebrospinal fluid. Next steps could include using the model to test therapeutic candidates for PTSD.</p> <p>SciBX 5(11); doi:10.1038/scibx.2012.294 Published online March 15, 2012</p>	Patent and licensing status unavailable	<p>Kaouane, N. <i>et al. Science</i>; published online Feb. 23, 2012; doi:10.1126/science.1207615 Contact: Aline Desmedt, Institut National de la Santé et de la Recherche Médicale (INSERM), Bordeaux, France e-mail: aline.desmedt@inserm.fr</p>

This week in techniques

Approach	Summary	Licensing status	Publication and contact information
Drug platforms			
Crystal structure of dihydropteroate synthase bound to sulfonamide antibiotics	The crystal structure of dihydropteroate synthase bound to sulfonamide antibiotics could aid the discovery of new antibiotics that overcome known resistance mutations. The cocrystal structure suggests that the thiazole and methoxazole rings of sulfonamide antibiotics are positioned where known resistance mutations at Phe33 and Pro69 could impede drug binding. Next steps include using the crystal structure to discover and rationally design small molecules that bind to other sites on the target.	Unpatented; licensing status not applicable	Yun, M.-K. <i>et al. Science</i> ; published online March 2, 2012; doi:10.1126/science.1214641 Contact: Stephen W. White, St. Jude Children's Research Hospital, Memphis, Tenn. e-mail: stephen.white@stjude.org
	SciBX 5(11); doi:10.1038/scibx.2012.295 Published online March 15, 2012		
Using sonic hedgehog homolog (SHH)-treated engineered blood vessels to improve bone formation	Mouse and <i>in vitro</i> studies suggest treating engineered blood vessels with SHH could help improve bone graft outcomes. In engineered blood vessels, addition of exogenous SHH increased formation of vascular lumen and total lumen area compared with no SHH addition. In mice, bone graft implants with SHH-treated vasculature led to better perfusion and formation of mature bone tissue than implants without SHH-treated vasculature. Next steps include testing the implant in large animal models.	Unpatented; licensing status not applicable	Rivron, N.C. <i>et al. Proc. Natl. Acad. Sci. USA</i> ; published online March 2, 2012; doi:10.1073/pnas.1117627109 Contact: Nicolas C. Rivron, University of Twente, Enschede, the Netherlands e-mail: nicolasrivron@gmail.com
	SciBX 5(11); doi:10.1038/scibx.2012.296 Published online March 15, 2012		
Markers			
Methylation of <i>ataxia telangiectasia mutated (ATM)</i> as a marker for breast cancer risk	Measuring DNA methylation of <i>ATM</i> in peripheral blood samples could help predict breast cancer risk. In peripheral blood samples from patients and healthy subjects, high levels of methylation at two <i>ATM</i> loci were associated with a greater risk for developing bilateral breast cancer. Next steps include developing a molecular signature based on <i>ATM</i> methylation that could help predict disease risk.	Patent and licensing information available from UCL Business plc Contact: Carol Harty, UCL Business plc, London, U.K. phone: +44 (0) 20 7679 9000 e-mail: c.harty@uclb.com	Brennan, K. <i>et al. Cancer Res.</i> ; published online Feb. 28, 2012; doi:10.1158/0008-5472.CAN-11-3157 Contact: James M. Flanagan, Imperial College London, London, U.K. e-mail: j.flanagan@imperial.ac.uk
	SciBX 5(11); doi:10.1038/scibx.2012.297 Published online March 15, 2012		

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Target and compound index

5-Hydroxymethyl-2-furfural 12
A
 α -Hemolysin 2
 A β 10
 AC-8632 9
 ACACB 9
 ACC2 9
 Acetyl-coenzyme A carboxylase- β 9
 Aes-103 12
 AMPA 1 glutamate receptor 11

Androgen 12
 AT008 8
 Ataxia telangiectasia mutated ATM 14

B
 β -Amyloid 10

C
 Cannabinoid CB₁ receptor 10
 CC chemokine receptor 4 8
 CCR4 8
 CD194 8
 Chemokine CXC motif ligand 16 11
 CNR1 10
 Collagen 6
 Corticosterone 13
 CXC chemokine receptor 6 11
 CXCL16 11
 CXCR6 11

D
 Dihydropteroate synthase 14
 DM-99 9
 DNAP 1

E
 EPRS 7

F
 Febrifugine 6
 Furan 8

G
 GLUR1 11
 Glutamyl-prolyl-tRNA synthetase 7
 Glycogen synthase kinase 3 β 9
 GRIA1 11
 GRIN1 11
 GSK3B 9

H
 Halofuginone 6
 HDAC 7
 Histone deacetylase 7
 HT-100 7

I
 IFN 5
 IL-22 11
 Integrin $\alpha_v\beta_6$ 7
 Integrin $\alpha_v\beta_8$ 10

J
 JD-2114 10

L
 LTA 5,10
 LTB 5,10
 Lymphotoxin 5
 Lymphotoxin- α 5,10

M
 Mogamulizumab 8

N
 Neu-120 9
 NF- κ B 9
 NFKB2 9
 NMDA receptor NR1 subtype 11
 NR1 11
 Nuclear factor of κ light polypeptide gene enhancer in B cells 2 p49/p100 9

O
 Oleanolic acid 13

P
 P2RX4 11
 P2X4 11
 p33 5,10
 p52 9
 PDE-7 8
 Peruvoside 12
 Phi29 DNA polymerase 1
 Phosphodiesterase-7 8
 Proteasome 11
 Purinergic receptor P2X ligand-gated ion channel 4 11

R
 RAR-related orphan receptor A 8
 Receptor tyrosine kinase 9
 RORA 8
 RTK 9

S
 Saponin 13
 SEMA3F 8
 Semaphorin 3F 8
 SHH 14
 Sonic hedgehog homolog 14
 STX-100 7
 Sulfonamide 14
 Sunitinib 9
 Sutent 9

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 Type I interferon 5