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# Fixing mitophagy in Parkinson's disease

By Kai-Jye Lou, Senior Writer

**Genentech Inc.** has identified ubiquitin specific peptidase 30 as a potentially disease-modifying target involved in the clearance of damaged mitochondria in Parkinson's disease.<sup>1</sup> The **Roche** unit now needs to determine whether the deubiquitinase is indeed druggable.

Mitophagy is a form of autophagy that involves ridding cells of damaged mitochondria and is one of the key pathways for maintaining mitochondrial quality control.<sup>2,3</sup> Defects in the process can result in the accumulation of damaged mitochondria within cells, leading to increased oxidative stress and cellular dysfunction.

Genetic studies have identified loss-of-function mutations in two regulators of mitophagy that are associated with PD.<sup>4,5</sup> One regulator is PTEN induced putative kinase 1 (PINK1), a mitochondria-targeted serine/threonine kinase, and the other is the E3 ubiquitin ligase parkin (PARK2).<sup>6,7</sup>

PINK1 recruits parkin to damaged mitochondria, which leads to parkin-mediated ubiquitination of mitochondrial proteins and mitophagy.

**Mitokinin LLC** has a PINK1 activator in preclinical development to treat PD. The rationale is that increasing PINK1 activity could rescue the impairments in mitophagy observed in PD.

Now, Genentech researchers have published a paper in *Nature* that identifies another way to target this pathway. The group linked ubiquitin specific peptidase 30 (USP30) to parkin-mediated mitophagy.

“Our study grew out of Parkinson's disease genetics that indicate defects in the mitophagy pathway—specifically the genes *PINK1* and *parkin*—cause familial Parkinson's disease in humans,” said Baris Bingol, the co-lead author on the study and a scientist at Genentech. “Given that parkin is an E3 ubiquitin ligase, we wondered if there is a deubiquitinating enzyme that counteracts parkin and inhibits mitophagy. USP30 hit the mark in a screen designed for identifying deubiquitinating enzymes that block mitophagy.”

After picking out USP30 from the screen, the team carried out a series of *in vitro* studies that showed the peptidase blocks mitophagy in dopaminergic neurons and deubiquitinates mitochondrial proteins that parkin ubiquitinates. The group also showed that parkin ubiquitinates USP30 and induces its degradation and that two different PD-associated parkin mutants lacked that activity. This result suggests that wild-type parkin removes a brake on mitophagy set by USP30 and that PD-associated parkin mutants fail to do this.

In neuronal cell lines expressing a PD-associated parkin mutant, siRNA against USP30 rescued mitophagy defects, whereas control

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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  
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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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siRNA did not. In fly models of PD in which the disease phenotype is caused by loss-of-function mutations in *pink1* or *parkin*, knockdown of *usp30* rescued the defects in mitophagy and improved motor function.

In flies treated with a PD-linked mitochondrial toxin, *usp30* knockdown improved motor function and survival.

“We believe USP30 inhibition offers a novel strategy by activating clearance of damaged, unhealthy mitochondria to boost mitochondrial quality control,” said Bingol.

He noted that USP30 inhibition could potentially offer a disease-modifying therapy that slows down or halts the progression of PD.

“If you could prevent the death of dopaminergic neurons with a USP30 inhibitor in patients with early Parkinson’s disease,

you could potentially extend the period where L-dopa remains effective,” said Mitokinin cofounder and CSO Nicholas Hertz.

“I think this approach could be a good idea to explore in Parkinson’s if they can find a molecule that is able to selectively inhibit USP30 and cross the blood brain barrier,” said Richard Youle, chief of the biochemistry section at the Surgical Neurology Branch of the NIH’s **National Institute of Neurological Disorders and Stroke**. He cautioned that the extent to which the PINK1-parkin pathway drives PD in humans is still unknown.

Moreover, the majority of human PD cases are idiopathic. PD cases with genetic origins account for about 5%–10% of total cases.<sup>8</sup>

**Mulling over mammals**

Before considering a possible drug discovery effort, Bingol said that the function of USP30 and safety of USP30 inhibition in mammals will need to be investigated.

Youle noted that studies in some mammalian models could be challenging. He said that mice with mutations in *Pink1* and *parkin* do not have a PD phenotype. Instead, he said, dogs with mitochondrial mutations might represent a better model system for evaluating USP30 inhibition.

Another option could be rats, added Kevan Shokat, chair of the Department of Cellular and Molecular Pharmacology at the **University of California, San Francisco** and a **Howard Hughes Medical Institute** investigator. Shokat also is a Mitokinin cofounder and a member of Genentech’s scientific resource board. He noted that *Pink1* knockout rats recapitulate a PD phenotype,<sup>9</sup> although *parkin* knockouts do not.

Hertz agreed that knockout rat studies could be a good option for studying USP30 inhibition. “If you saw that knocking out *Usp30* in rats does not result in a developmental phenotype, that result suggests that USP30 inhibition could be achieved without deleterious effects,” he said. “One would then want to know if knocking out *Usp30* could rescue the Parkinson’s disease phenotype in the rat model.”

Hertz said that another important next step will be to screen human populations for mutations in *USP30* and then determine whether those individuals are at lower risk of PD.

**“We believe USP30 inhibition offers a novel strategy by activating clearance of damaged, unhealthy mitochondria to boost mitochondrial quality control.”**

**—Baris Bingol, Genentech Inc.**

**“I think this approach could be a good idea to explore in Parkinson’s if they can find a molecule that is able to selectively inhibit USP30 and cross the blood brain barrier.”**

—Richard Youle,  
National Institute of  
Neurological Disorders and  
Stroke

Although the druggability of USP30 remains to be determined, Bingol said that there is some precedent to suggest that deubiquitinating enzymes could be targeted with small molecules.

“For example, inhibitors for USP1, USP7 [HAUSP] and USP14 [TGT] have already been described. However, biophysical characterization, pharmacokinetic experiments and medicinal chemistry optimization will be required

for these published inhibitors to be considered viable leads for drug discovery. These types of studies will help determine whether deubiquitinating enzymes, including USP30, are druggable as a class,” Bingol told *SciBX*.

Beyond PD, Youle noted that there also could also be opportunities for USP30 inhibitors in other diseases caused by mitochondrial dysfunction such as Leber hereditary optic neuropathy.

Genentech declined to provide details of its programs in PD or disclose the patent and licensing status related to the data described in *Nature*.

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#### REFERENCES

1. Bingol, B. *et al. Nature*; published online June 4, 2014; doi:10.1038/nature13418  
**Contact:** Baris Bingol, Genentech Inc., South San Francisco, Calif.  
e-mail: [bingol.baris@gene.com](mailto:bingol.baris@gene.com)
2. Narendra, D.P. & Youle, R.J. *Antioxid. Redox Signal.* **14**, 1929–1938 (2011)
3. Palikaras, K. & Tavernarakis, N. *Exp. Gerontol.* **56**, 182–188 (2014)
4. Kitada, T. *et al. Nature* **392**, 605–608 (1998)
5. Valente, E.M. *et al. Science* **304**, 1158–1160 (2004)
6. Narendra, D. *et al. J. Cell Biol.* **183**, 795–803 (2008)
7. Chan, N.C. *et al. Hum. Mol. Genet.* **20**, 1726–1737 (2011)
8. Lesage, S. & Brice, A. *Hum. Mol. Genet.* **18**, R48–R59 (2009)
9. Ramboz, S. *et al. Neuromuscular Disord.* **23**, 836 (2013)

#### COMPANIES AND INSTITUTIONS MENTIONED

**Genentech Inc.**, South San Francisco, Calif.

**Howard Hughes Medical Institute**, Chevy Chase, Md.

**Mitokinin LLC**, New York, N.Y.

**National Institute of Neurological Disorders and Stroke**, Bethesda, Md.

**National Institutes of Health**, Bethesda, Md.

**Roche** (SIX:ROG; OTCQX:RHHBY), Basel, Switzerland

**University of California, San Francisco**, Calif.



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# Partnering in pediatrics

By Amy Donner, Senior Editor

**Alexion Pharmaceuticals Inc.** is hoping that its research collaboration with **Cincinnati Children's Hospital Medical Center** will help the biotech build out a rare disease pipeline that currently is dominated by a single molecule—Soliris eculizumab. The deal is Alexion's first collaboration with a clinical center and complements its pipeline-building efforts with biotech and academia.

For CCHMC, the deal brings the first infusion of corporate dollars into its two-year-old innovation fund.

Under the deal, Alexion will fund rare disease research programs at the hospital and will have an exclusive option to license completed programs. If Alexion exercises an option, it would be responsible for clinical development and commercialization, and the CCHMC would be eligible for milestones and royalties.

Further financial details were not disclosed, but Alexion established the Alexion Rare Disease Innovation Fund within the hospital's existing Innovation Fund.

Niki Robinson, assistant VP of CCHMC's Center for Technology Commercialization (CTC), said that the Innovation Fund was

established in 2012 to help make hospital discoveries more commercially viable. The fund is managed by the CTC.

"Awardees don't just get funding," she said. "They also get mentors and a commercially driven milestone plan before the work gets started."

The goal is to get the projects to a commercial point within two years.

Proposals are vetted by an advisory board consisting of 20 experts in drug discovery or devices, angel investors and VCs. Half of the members of the advisory board are affiliated with CCHMC, and the others are external.

Grants are evaluated based on five criteria: significance or clinical impact, commercial potential, novelty (including IP considerations), feasibility and impact on the mission of the hospital.

The program has funded 16 projects in 3 years (see Table 1, "Innovation Fund award recipients"), resulting in 24 patents and 24 partner agreements that include industry-sponsored research, matching funds, options or licenses, and confidentiality agreements.

In 2014, the hospital spun out its first company related to an Innovation Fund award. **Persepsys Biomedical LLC** was

formed based on a project led by Hector Wong. The startup is focused on sepsis. Wong is a professor of pediatrics and director of critical care medicine at CCHMC.

The Innovation Fund has provided about \$1 million to the projects per year. Until now, that money has come solely from CCHMC internal sources.

**"We are considering projects that show significant promise in providing life-transforming benefits to patients with devastating disorders. When it comes to therapeutic areas, we are agnostic."**

—Kim Diamond,  
Alexion Pharmaceuticals Inc.

**Table 1. Innovation Fund award recipients.** The Innovation Fund is managed by **Cincinnati Children's Center for Technology Commercialization**.

Source: Cincinnati Children's Center for Technology Commercialization

Principal investigator	Indication	Summary (status)
<b>2012</b>		
John Pestian	Neurology	Markers as a predictor of repeated suicide attempts (Optioned to <b>Assurex Health Inc.</b> )
Margaret Hostetter	Infectious disease	Peptide vaccines and antibodies to prevent central line infections
Michael Seid; Peter Margolis	Not applicable	Collaborative chronic care (C3N) portal for personalized collaborative care (in due-diligence stage to form start up)
John Perentesis	Not applicable	Next-generation clinical trials management software
Hector Wong	Hepatic disease	Pediatric sepsis biomarker risk model (launched <b>Persepsys Biomedical LLC</b> in 2014 to create products that prevent death from sepsis or septic shock)
Marie-Dominique Filippi; Yi Zheng	Inflammation	Anti-inflammatory drug targeting NADPH oxidase 2 (NOX2) in acute lung injury
<b>2013</b>		
Lee (Ted) Denson	Gastrointestinal disease	Markers to diagnose inflammatory bowel disease (IBD), Crohn's disease and ulcerative colitis (UC)
Charles Dumoulin	Imaging	Neonatal MRI scanner (in due-diligence stage to form start up)
William Hardie	Pulmonary disease	Therapy to reverse pulmonary fibrosis
Punam Malik	Hematology	<i>Hemoglobin-γ</i> gene therapy to treat sickle cell disease
Senthil Sadhasivam	Neurology	Point-of-care gene chip to dose opioids for pain management in perioperative patients
Hector Wong	Hepatic disease	IL-27 as a biomarker for early identification of patients with sepsis
<b>2014</b>		
Prasad Devarajan; Hermine Brunner	Autoimmune disease; renal disease	Blood test to detect the onset of kidney failure in patients with lupus
H. Leighton Grimes	Cancer	Small molecule targeting signal transducer and activator of transcription 5 (STAT5)
Michael Jordan	Autoimmune disease	Targeted, activated immune cells to suppress undesirable immune response
Ming Tan	Infectious disease	Vaccine for norovirus, rotavirus, hepatitis E virus and astrovirus

**Enter Alexion**

Rather than forming a new initiative, the Alexion Rare Disease Innovation Fund will piggyback on the existing Innovation Fund. The advisory board will be expanded to include representatives from Alexion.

“They will pick and fund their own projects,” said Robinson. In this regard, she noted, Alexion’s advisory board members will be more akin to partners than advisors.

“We are considering projects that show significant promise in providing life-transforming benefits to patients with devastating disorders,” said Alexion spokesperson Kim Diamond. “When it comes to therapeutic areas, we are agnostic.”

As with the other Innovation Fund projects, funding levels will be project specific. Robinson said that funding levels are determined at the end of a process during which the scope and scale of a project often evolves based on the commercialization plan.

The first projects chosen by Alexion in the collaboration with CCHMC will begin in July 2015.

The hospital is one of the largest for pediatric patients in the country and thus has access to a significant number of rare disease cases. “We see a lot of patients with rare disease, and the new fund aligns our two organizations based on our common interest in rare disease,” said Robinson.

The collaboration with CCHMC is the first of this kind for the biotech. Until now, Alexion has partnered with other companies, academia and independent investigators, but it has not worked directly with a hospital to fund the commercial transition of selected projects.

In February, Alexion gained an exclusive option to acquire **Prothelia Inc.**, a rare-disease company developing PRT-01 to treat merosin-deficient congenital muscular dystrophy type 1A (MDC1A), and to license PRT-01 directly from the **University of Nevada, Reno**. PRT-01 is

**“We see a lot of patients with rare disease, and the new fund aligns our two organizations based on our common interest in rare disease.”**

**—Niki Robinson,  
Cincinnati Children’s Hospital  
Medical Center**

laminin-111 protein replacement therapy that Prothelia had licensed from the university. The compound has orphan drug designation in the U.S. to treat MDC1A and Duchenne muscular dystrophy.

In January, Alexion formed an exclusive strategic agreement with **Moderna Therapeutics Inc.** to develop mRNA therapeutics to treat rare diseases. The deal includes a \$100 million upfront payment for

10 product options. Alexion will lead the discovery, development and commercialization of those products, while Moderna will design and manufacture them.

Alexion markets Soliris, a humanized anti-complement 5 (C5) mAb, to treat atypical hemolytic uremic syndrome (aHUS) and paroxysmal nocturnal hemoglobinuria (PNH). Eculizumab has orphan drug status for both indications in the U.S., Europe and Switzerland, for aHUS in Australia and for PNH in Japan. The drug also is in clinical trials for a host of rare disease indications.

Alexion’s pipeline also includes Asfotase alfa, which is in registration for hypophosphatasia (HPP)—an inherited, ultra-rare metabolic condition characterized by defective bone mineralization. Asfotase alfa is a fusion between a bone-targeting peptide and the catalytic domain of human tissue non-specific alkaline phosphatase (TNSALP; ALPL).

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**COMPANIES AND INSTITUTIONS MENTIONED**

**Alexion Pharmaceuticals Inc.** (NASDAQ:ALXN), Cheshire, Conn.

**Cincinnati Children’s Hospital Medical Center**, Cincinnati, Ohio

**Moderna Therapeutics Inc.**, Cambridge, Mass.

**Persepsys Biomedical LLC**, Cincinnati, Ohio

**Prothelia Inc.**, Milford, Mass.

**University of Nevada, Reno**, Nev.

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# New route for old cancer agents

By Tracey Baas, Senior Editor

Researchers at the **University of Wisconsin–Madison** and **Collectar Biosciences Inc.** have exploited differences in lipid architecture between cancer and normal cells to create compounds that deliver radiolabels selectively to different types of malignant cells while sparing healthy ones.<sup>1</sup>

The group has started multiple clinical trials of its agents for imaging, radiotherapy and intraoperative tumor margin detection.

Cancer cells were first shown to differ in lipid uptake from normal cells over four decades ago through studies on phospholipid ethers.<sup>2–4</sup> About 20 years later, researchers at the **University of Michigan** looked for imaging uses of the findings by investigating how chemical alterations of aryl phospholipid ethers and alkylphosphocholines affected the compounds' uptake and retention in tumors.<sup>5–7</sup>

Those studies were led by Raymond Counsell and his graduate students, including Jamey Weichert. In 2006, the duo developed the tumor imaging agent 18-(p-iodophenyl) octadecyl phosphocholine (CLR1404),<sup>8</sup> which selectively accumulated in tumors and showed low toxicity in rats.

Now, a team co-led by Weichert and John Kuo at the University of Wisconsin–Madison found that linking the cancer homing properties of CLR1404 with radioiodine or fluorescent or near-infrared labels did not diminish its selective uptake and retention in tumors. They also showed CLR1404 uptake and retention in therapeutically resistant cancer stem cells. Indeed, the results suggested that CLR1404 could deliver radioisotopes or other chemical groups to cancer and cancer stem cells in many different malignancies and could serve as a scaffold for generating diagnostic or therapeutic agents.

Weichert is now an associate professor of radiology, medical physics and pharmaceuticals at UW-Madison and founder and CSO of cancer company Collectar. Kuo is an associate professor of neurological surgery and human oncology and director of the Comprehensive Brain Tumor Program at the **University of Wisconsin School of Medicine and Public Health**.

Incubation of fluorescently labeled or radioiodinated CLR1404 showed three- to ninefold greater uptake in multiple human cancer cell lines than in matched human normal cell lines. In patient-derived cell lines, fluorescently labeled CLR1404 showed higher uptake in human glioblastoma stem-like cell lines than in normal fetal neural stem cells.

Conversely, pretreatment with filipin III, an agent that disrupts lipid rafts and sequesters cholesterol, reduced uptake by about 40%. The team concluded that CLR1404 uses lipid rafts as a major portal into cancer cells.

Next, the team explored the imaging and therapeutic potential of the CLR1404 scaffold using two different iodine radioisotopes in mouse models of 57 different types of cancer.

In genetic tumor or xenograft mouse models, PET imaging detected <sup>124</sup>I-CLR1404 in primary or metastatic tumors but not in benign or premalignant tumors or in inflammatory or premalignant lesions.

Because <sup>131</sup>I is a well-established cytotoxic radioisotope, the team tested the therapeutic potential of <sup>131</sup>I-CLR1404.

In xenograft mouse models of cancer, a single dose of 100–145 microcuries of <sup>131</sup>I-CLR1404 decreased tumor growth and increased survival compared with a dose of unlabeled CLR1404. In radioresistant uterine sarcoma and glioma mouse models, two doses achieved similar effects.

Finally, the researchers started multiple Phase I/Ib PET imaging trials and reported examples of radiolabeled CLR1404 imaging from the first three patients.

In a patient with non-small cell lung cancer (NSCLC) and a patient with glioma, PET imaging of <sup>124</sup>I-CLR1404 clearly visualized tumors throughout the brain and body. In the third patient, who had colorectal cancer, single-photon emission computed tomography using <sup>131</sup>I-CLR1404 showed uptake and retention of the compound in the tumor and in metastases. Successful imaging agent detection of brain metastases suggested that the compounds can cross the blood brain barrier.

Results were published in *Science Translational Medicine*.

Kuo told *SciBX* that preliminary follow-up results in patients with end-stage cancer treated with <sup>131</sup>I-CLR1404 showed disease stabilization with a low side effect profile.

One size might fit all

The broad-spectrum approach of targeting cancer cells based on their lipid composition could be an effective strategy for developing imaging and therapeutic agents.

**“There’s a long history of studies that show lipid compounds selectively accumulate in cancer cells, but how that occurs and how lipid rafts contribute to that uptake remains to be determined.”**

—Matt Vander Heiden,  
Massachusetts Institute of  
Technology

“People are starting to remember how useful conventional chemotherapies are to treat a variety of different cancers,” said Matt Vander Heiden, an associate professor of biology at the Koch Institute for Integrative Cancer Research at the **Massachusetts Institute of Technology**.

Marcel Verheij, chair of the Department of Radiotherapy at the **Netherlands Cancer Institute** and a professor at the **Free University Amsterdam**, noted that CLR1404 itself could be used to optimize patient selection.

“This broad-spectrum approach is different from the trial-and-error strategy that has been used in the past for conventional chemotherapy,” he said. “By first identifying which tumors incorporate the imaging variant of CLR1404, a preselection of patients with a high chance of responding to the therapeutic variant becomes possible.”

He added, “The preselection offers the opportunity to avoid exposing patients with poor uptake to the possible side effects. This strategy could also allow for a better staging of patients by visualizing sites of metastatic disease and for identifying residual disease following surgery or other local treatments.”

Julie Novak, VP of research and project management at cancer imaging company **Blaze Bioscience Inc.**, agreed. “Having a companion imaging agent can be helpful in selection of patients if the specificity

**“We are always looking for a one-size-fits-all therapeutic-diagnostic agent as it limits costs for clinical translation, has a broader applicability and a more well-known pharmacokinetic-pharmacodynamic profile.”**

—Gooitzen van Dam,  
University of Groningen

of both agents proves to be similar in human cancer patients. Positive imaging data may not correlate with therapeutic utility, but negative imaging data might be useful in excluding patients in trials with little chance of benefiting from the therapy,” she said.

Vander Heiden wanted to see more mechanistic details of the preferential uptake of the analogs into cancer cells over normal cells. “There’s a long history

of studies that show lipid compounds selectively accumulate in cancer cells, but how that occurs and how lipid rafts contribute to that uptake remains to be determined,” he said. He added that these mechanistic studies should include tumor cells, normal cells and rapidly proliferating normal cells that often contribute to toxicity profiles.

According to Novak, one of the key opportunities for the PLE approach may be in imaging during cancer surgery, though little data are provided in the paper for the intraoperative imaging compound.

“The team will ultimately have to show in a clinical setting that the agents improve surgeons’ ability to distinguish tumor from nontumor tissues,” Novak added. “This boils down to contrast at the time of surgery—the higher the contrast achieved, the more easily the surgeon can make a call.”

She said that it would be important to show “consistent uptake in tumor tissue, retention by the tumor, clearance from normal tissues within an acceptable time post-dose and brightness that enables detection by imaging devices within their dynamic range.”

In addition, she cautioned that the overlap between cancer pathways and inflammatory or other disease processes can cause some

tumor imaging agents to label nontumor tissues, a process that could compromise effectiveness in surgery.

According to Gooitzen van Dam, the dual therapeutic-diagnostic potential is a significant advantage. “We are always looking for a one-size-fits-all therapeutic-diagnostic agent as it limits costs for clinical translation, has a broader applicability and a more well-known pharmacokinetic-pharmacodynamic profile.” van Dam is a professor of surgery and head of the Intraoperative Imaging Research Group at the **University of Groningen**.

CLR1404 and radioisotope analogs were first patented in 2001 by the University of Michigan and Collectar. Collectar patented the fluorescent analogs in 2012 and has subsequently filed patent applications for diagnostic and therapeutic use of all compounds. The team is open to discussing partnering opportunities.

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#### REFERENCES

1. Weichert, J.P. *et al. Sci. Transl. Med.*; published online June 11, 2014; doi:10.1126/scitranslmed.3007646  
**Contact:** John S. Kuo, University of Wisconsin School of Medicine and Public Health, Madison, Wis.  
e-mail: [j.kuo@neurosurgery.wisc.edu](mailto:j.kuo@neurosurgery.wisc.edu)  
**Contact:** Jamey P. Weichert, Collectar Biosciences Inc., Madison, Wis.  
e-mail: [jweichert@uwhealth.org](mailto:jweichert@uwhealth.org)
2. Snyder, F. *et al. Biochim. Biophys. Acta* **176**, 502–510 (1969)
3. Snyder, F. & Wood, R. *Cancer Res.* **29**, 251–257 (1969)
4. Soodma, J.F. *et al. Cancer Res.* **30**, 309–311 (1970)
5. Rampy, M.A. *et al. J. Med. Chem.* **38**, 3156–3162 (1995)
6. Meyer, K.L. *et al. J. Med. Chem.* **32**, 2142–2147 (1989)
7. Rampy, M.A. *et al. J. Nucl. Med.* **37**, 1540–1545 (1996)
8. Pinchuk, A.N. *et al. J. Med. Chem.* **49**, 2155–2165 (2006)

#### COMPANIES AND INSTITUTIONS MENTIONED

**Blaze Bioscience Inc.**, Seattle, Wash.  
**Collectar Biosciences Inc.** (OTCQX:CLRBD), Madison, Wis.  
**Free University Amsterdam**, Amsterdam, the Netherlands  
**Massachusetts Institute of Technology**, Cambridge, Mass.  
**Netherlands Cancer Institute**, Amsterdam, the Netherlands  
**University of Groningen**, Groningen, the Netherlands  
**University of Michigan**, Ann Arbor, Mich.  
**University of Wisconsin School of Medicine and Public Health**, Madison, Wis.  
**University of Wisconsin–Madison**, Madison, Wis.

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# Hedgehog joins the resistance

By Lev Osherovich, Senior Writer

Increased glucuronidation by activated hedgehog signaling turns out to be the root of drug resistance for at least two compounds in acute myeloid leukemia.<sup>1</sup> Inhibiting the pathway could avoid the toxicity of general glucuronidase suppression and boost the efficacy of standard acute myeloid leukemia therapies.

The Canadian team behind the study now plans to test a combination of ribavirin, a chemotherapeutic nucleoside analog, with an inhibitor of smoothened (SMO), a druggable player in the hedgehog pathway.

Glucuronidation by UDP glucuronosyltransferase (UGT) enzymes represents one of the key metabolic clearance mechanisms used by the liver to eliminate drugs.

Although cancer cells are well known to develop drug resistance through overexpression of P glycoprotein (MDR1; ABCB1; P-gp; CD243)—an efflux pump involved in drug disposition—this is the first report of cancer cells hijacking UGT enzymes to nullify drugs.

“The link between the glucuronosyltransferase and AML was a complete surprise to us,” said Katherine Borden, lead author on the study. “These enzymes have been known since the 1950s, and people think of them as being important in steady-state drug metabolism in the liver. The idea that glucuronidation could be evolved by a cancer cell to neutralize a drug is totally new.” Borden is a professor of pathology and cell biology at the **University of Montreal**.

Her team found the connection when they noted that all initial responders in a Phase II acute myeloid leukemia (AML) trial of ribavirin monotherapy subsequently relapsed. Ribavirin was provided by Canadian generics maker **Pharmascience Inc.**, which also participated in the new study.

To investigate what might explain the relapse, Borden’s group created resistant cells from cancer cell lines that normally respond to ribavirin. In the resistant cells, ribavirin no longer interacted with its target, eukaryotic translation initiation factor 4E (eIF4E).

Next, the team sequenced mRNA from drug-resistant cells and saw higher levels of *glioma-associated oncogene homolog 1 zinc finger protein (GLI1)* than those in ribavirin-sensitive controls. *GLI1* mRNA levels also were greater in leukemic cells from relapsed patients with AML than in responding patients or healthy controls.

*In vitro*, overexpression of *GLI1* induced resistance to both ribavirin and cytarabine—another drug associated with resistance in AML—whereas siRNA knockdown of *GLI1* restored sensitivity to both drugs.

GLI1 is a transcription factor involved in hedgehog signaling. To find what was driving the GLI1-induced resistance, the team looked upstream in the signaling pathway and found that the SMO inhibitor Erivedge vismodegib restored sensitivity to both ribavirin and cytarabine.

Erivedge is marketed by **Roche** for basal cell carcinoma (BCC). Erivedge and at least five other inhibitors of hedgehog signaling, including **Pfizer**

Inc.’s PF-04449913, are in various stages of clinical testing for a range of cancers.

Finally, Borden’s team looked for the target of GLI1 responsible for drug resistance. They noted that levels of eIF4E remained elevated in ribavirin-resistant cells despite the protein’s inability to associate with the drug. That suggested GLI1 might have modified the ribavirin target.

The team looked at drug-metabolizing enzymes and found higher levels of UDP glucuronosyltransferase 1 family polypeptide A1 (UGT1A1) in resistant cells than in controls. Those levels were decreased by *GLI1* knockdown. In addition, both ribavirin and cytarabine were glucuronidated in resistant cells, and inhibition of hedgehog signaling with Erivedge eliminated ribavirin glucuronidation.

Borden and colleagues concluded that GLI1 promotes resistance to ribavirin and cytarabine by stimulating UGT1A1 activity to glucuronidate the drugs and prevent them from interacting with their target.

Results were reported in *Nature*.

## Metabolic resistance

Borden’s study is the latest example of how the hedgehog pathway helps cancers evade therapeutics, but this is the first time the pathway has turned up as a driver of drug metabolism.

“Here, hedgehog signaling clearly contributes to removal of the drug,” said Tannishtha Reya, a professor of pharmacology at the **University of California, San Diego**. Reya led a team that discovered the involvement of the hedgehog pathway in drug-resistant chronic myeloid leukemia (CML).<sup>2</sup>

The hedgehog-dependent mechanism of CML drug resistance does not appear to involve glucuronidation.

The hedgehog pathway “is clearly integral to the evolution of drug resistance, and an inhibitor of this pathway could extend survival,” she added.

Borden’s findings argue for combining inhibitors of hedgehog signaling with conventional chemotherapy to combat drug resistance in AML. Along those lines, Pfizer is testing PF-04449913 in combination with cytarabine and other chemotherapeutics in an

open-label Phase Ib/II trial.

Borden and Pharmascience have filed for authorization in Canada to repeat their ribavirin AML trial in combination with a hedgehog pathway inhibitor such as Erivedge. **Genentech Inc.**, the Roche unit that developed Erivedge along with partner **Curis Inc.**, declined to comment on Borden’s study.

Stephen Morris, senior director of research and innovative drug development at Pharmascience, said that his company played a supporting role in Borden’s study and might play a more active role in Borden’s planned combination trial.

“We stumbled into this,” said Morris. “Borden approached us some time ago to test her hypothesis that ribavirin could be useful for treating AML. Borden and her clinical collaborators noticed the emergence of resistance in the trial. Our contribution was to determine that the drug was being modified by glucuronidation.” Morris said that it would be worthwhile to study whether hedgehog-mediated glucuronidation occurs in other tumor types or with other chemotherapeutics besides cytarabine and ribavirin.

**“The link between the glucuronosyltransferase and AML was a complete surprise to us. The idea that glucuronidation could be evolved by a cancer cell to neutralize a drug is totally new.”**

—Katherine Borden,  
University of Montreal

Meanwhile, Borden wants to know whether inhibiting glucuronidation directly, rather than by hitting hedgehog signaling, could overcome resistance.

“We’re also interested in targeting glucuronosyltransferases themselves,” said Borden. “This is a family of ten enzymes, but we think that only a subset is responsible for drug resistance. We’re trying to set up an NMR-based fragment screen for glucuronosyltransferase inhibitors.”

Borden has filed a patent on the use of hedgehog pathway inhibitors to prevent drug resistance in AML. The patent, which is co-owned by Pharmascience, is available for licensing.

Osherovich, L. *SciBX* 7(27); doi:10.1038/scibx.2014.785  
Published online July 17, 2014

#### REFERENCES

1. Zahreddine, H.A. *et al. Nature*; published online May 28, 2014; doi:10.1038/nature13283  
**Contact:** Katherine L.B. Borden, University of Montreal, Montreal, Quebec, Canada  
e-mail: [katherine.borden@umontreal.ca](mailto:katherine.borden@umontreal.ca)
2. Zhao, C. *et al. Nature* **458**, 776–779 (2009)

#### COMPANIES AND INSTITUTIONS MENTIONED

**Curis Inc.** (NASDAQ:CRIS), Lexington, Mass.  
**Genentech Inc.**, South San Francisco, Calif.  
**Pfizer Inc.** (NYSE:PFE), New York, N.Y.  
**Pharmascience Inc.**, Montreal, Quebec, Canada  
**Roche** (SIX:ROG;OTCQX:RHHBY), Basel, Switzerland  
**University of California, San Diego**, La Jolla, Calif.  
**University of Montreal**, Montreal, Quebec, Canada

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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>				
Inflammatory bowel disease (IBD)	IL-9	<p>Studies in human samples and mice suggest antagonizing IL-9 could help treat IBD. In samples from patients with ulcerative colitis (UC), <i>IL-9</i> expression was higher than that in samples from healthy controls and was associated with active disease. In a mouse model of UC, <i>IL-9</i> knockout decreased weight loss, proinflammatory cytokine expression and mucosal inflammation compared with no alteration. In the mouse model, an anti-IL-9 antibody decreased body weight loss and colitis severity compared with an isotype control antibody. Next steps include assessing expression of <i>IL-9</i> in patients who are refractive to anti-tumor necrosis factor (TNF) therapy and testing the effects of IL-9 on mucosal healing.</p> <p><b>SciBX 7(27); doi:10.1038/scibx.2014.786</b> Published online July 17, 2014</p>	Unpatented; licensing status not applicable	<p>Gerlach, K. <i>et al. Nat. Immunol.</i>; published online June 8, 2014; doi:10.1038/ni.2920</p> <p><b>Contact:</b> Markus F. Neurath, University of Erlangen-Nuremberg, Erlangen, Germany e-mail: <a href="mailto:markus.neurath@uk-erlangen.de">markus.neurath@uk-erlangen.de</a></p>
<b>Cancer</b>				
Acute lymphoblastic leukemia (ALL)	Cyclin dependent kinase 7 (CDK7)	<p><i>In vitro</i> and mouse studies have identified allosteric, covalent inhibitors of CDK7 that could help treat cancers including ALL. Cell-based screening and kinase selectivity profiling led to the identification of THZ1, a phenylaminopyrimidine that inhibited CDK7 at nanomolar concentrations. In ALL cell lines and xenograft mice, THZ1 decreased cell proliferation compared with an inactive control compound. In ALL cells, concentrations of THZ1 that did not affect global transcription were able to downregulate expression of runt-related transcription factor 1 (RUNX1), a driver of leukemia. Next steps at Syros Pharmaceuticals Inc. include testing CDK7 inhibitors in additional cancer models.</p> <p><b>SciBX 7(27); doi:10.1038/scibx.2014.787</b> Published online July 17, 2014</p>	Patent application filed; exclusively licensed to Syros Pharmaceuticals	<p>Kwiatkowski, N. <i>et al. Nature</i>; published online June 22, 2014; doi:10.1038/nature13393</p> <p><b>Contact:</b> Nathanael S. Gray, Dana-Farber Cancer Institute, Boston, Mass. e-mail: <a href="mailto:nathanael_gray@dfci.harvard.edu">nathanael_gray@dfci.harvard.edu</a></p> <p><b>Contact:</b> Richard A. Young, Whitehead Institute for Biomedical Research, Cambridge, Mass. e-mail: <a href="mailto:young@wi.mit.edu">young@wi.mit.edu</a></p>

## This week in therapeutics (continued)

Indication	Target/marker/pathway	Summary	Licensing status	Publication and contact information
B cell lymphoma	B cell lymphoma 2 (BCL-2; BCL2); cyclin dependent kinase 4 (CDK4); cyclin dependent kinase inhibitor 2A (CDKN2A; INK4a; ARF; p16INK4a); CDKN2B (INK4B; MTS2); retinoblastoma 1 (RB1)	<p>Patient and mouse studies suggest combined inhibition of CDK4 and BCL2 could help treat high-risk follicular lymphomas with mutations in the retinoblastoma pathway. In patients with indolent follicular lymphoma, genomic alterations in members of the retinoblastoma pathway including <i>CDKN2A</i>, <i>CDKN2B</i>, <i>RB1</i> and <i>CDK4</i> were associated with high-risk disease. In mouse xenograft models of follicular lymphoma with elevated RB1 phosphorylation, a combination of small molecule inhibitors of CDK4 and BCL2 decreased tumor growth compared with either inhibitor alone. Next steps could include evaluating the combination in additional types of B cell lymphomas with mutations in the retinoblastoma pathway.</p> <p>Pfizer Inc. and Amgen Inc. have the oral small molecule CDK4 and CDK6 inhibitor PD-0332991 in Phase III testing to treat breast cancer.</p> <p>Novartis AG and Otsuka Pharmaceutical Co. Ltd. have the CDK4 and CDK6 inhibitor LEE011 in Phase III testing for the same indication.</p> <p>At least two other companies have dual inhibitors of CDK4 and CDK6 in Phase II or earlier testing to treat various cancers.</p> <p>At least 12 companies have BCL2 inhibitors in Phase II or earlier testing to treat various cancers.</p> <p><b>SciBX 7(27); doi:10.1038/scibx.2014.788</b>  <b>Published online July 17, 2014</b></p>	Patent and licensing status unavailable	<p>Oricchio, E. <i>et al. J. Exp. Med.</i>; published online June 9, 2014; doi:10.1084/jem.20132120</p> <p><b>Contact:</b> Hans-Guido Wendel, Memorial Sloan-Kettering Cancer Center, New York, N.Y.  e-mail: <a href="mailto:wendelh@mskcc.org">wendelh@mskcc.org</a></p>
Breast cancer	Neuromedin U (NMU); HER2 (EGFR2; ErbB2; neu)	<p>Cell culture and mouse studies suggest inhibiting NMU could help treat HER2 inhibitor-resistant breast cancer. In human breast cancer cells, elevated NMU levels were associated with poor clinical outcomes and resistance to HER2 inhibitors. In HER2<sup>+</sup> human breast cancer cell lines treated with a HER2 inhibitor, NMU-targeting siRNA decreased proliferation and invasiveness compared with scrambled siRNA. In mice injected with a human breast cancer cell line resistant to Tykerb lapatinib, pretreatment of cells with NMU-targeting shRNA decreased tumor growth and metastases and increased survival compared with no pretreatment. Future studies could include identifying and testing pharmacological NMU inhibitors in HER2 inhibitor-resistant cancers.</p> <p>GlaxoSmithKline plc and Eddingpharm Inc. market Tykerb lapatinib, an inhibitor of epidermal growth factor receptor 1 (EGFR1; HER1; ErbB1) and HER2, to treat breast cancer. The drug is in Phase III testing to treat head and neck cancer and gastric cancer and Phase II trials to treat brain and liver cancers.</p> <p>Roche and its Genentech Inc. and Chugai Pharmaceutical Co. Ltd. units market Herceptin trastuzumab, a humanized mAb against HER2, to treat breast and gastric cancers.</p> <p>Boehringer Ingelheim GmbH markets Gilotrif afatinib, a dual inhibitor of HER1 and HER2, to treat non-small cell lung cancer (NSCLC). The drug is in Phase III testing to treat breast cancer and head and neck cancer and Phase I trials to treat solid tumors.</p> <p><b>SciBX 7(27); doi:10.1038/scibx.2014.789</b>  <b>Published online July 17, 2014</b></p>	Patent and licensing status unavailable	<p>Rani, S. <i>et al. Cancer Res.</i>; published online May 29, 2014; doi:10.1158/0008-5472.CAN-13-2053</p> <p><b>Contact:</b> Lorraine O'Driscoll, Trinity College Dublin, Dublin, Ireland  e-mail: <a href="mailto:lodrisc@tcd.ie">lodrisc@tcd.ie</a></p>

## This week in therapeutics (continued)

Indication	Target/marker/pathway	Summary	Licensing status	Publication and contact information
Cancer	CTLA-4 (CD152); signal transducer and activator of transcription 3 (STAT3)	<p><i>In vitro</i> and mouse studies suggest a CTLA-4-binding aptamer linked to STAT3 siRNA could help treat cancer. An aptamer was designed that binds to Ctlα-4 and is linked to Stat3 siRNA. In mouse models of melanoma, colorectal cancer, lymphoma and renal cell carcinoma, the aptamer-siRNA conjugate increased antigen-specific antitumor immunity and decreased tumor growth compared with a control aptamer-siRNA conjugate or vehicle. Next steps include clinical development of the aptamer-siRNA conjugate.</p> <p>Bristol-Myers Squibb Co. markets the CTLA-4 mAb Yervoy ipilimumab to treat melanoma. At least two other companies have therapeutics targeting CTLA-4 in Phase II or earlier testing. Isis Pharmaceuticals Inc. and AstraZeneca plc have ISIS-STAT3Rx, an antisense oligonucleotide targeting STAT3, in Phase I/II testing to treat cancer.</p> <p><b>SciBX 7(27); doi:10.1038/scibx.2014.790</b>  <b>Published online July 17, 2014</b></p>	Provisional patent filed; available for licensing	<p>Herrmann, A. <i>et al. J. Clin. Invest.</i>; published online June 2, 2014;  doi:10.1172/JCI73174  <b>Contact:</b> Hua Yu, City of Hope Comprehensive Cancer Center, Duarte, Calif.  e-mail:  <a href="mailto:hyu@coh.org">hyu@coh.org</a></p>
Cancer	Not applicable	<p>Mouse and human studies suggest radioiodinated alkylphosphocholine analogs containing <sup>131</sup>I or <sup>124</sup>I could be used to treat and image tumors, respectively. In xenograft mouse models of cancer, i.v. infusion of <sup>131</sup>I-CLR1404 decreased tumor growth and increased survival compared with unlabeled CLR1404. In genetic and xenograft mouse models of various cancers, the analog <sup>124</sup>I-CLR1404 could be imaged by PET in primary and metastatic tumors but showed little uptake by benign and premalignant tumors. In a patient with non-small cell lung cancer (NSCLC) and a patient with glioma, tumors and metastases were visualized with PET using <sup>124</sup>I-CLR1404. Ongoing work includes evaluating the blood brain barrier permeability of the analogs and designing clinical trials to evaluate the compounds for imaging, radiotherapy and intraoperative tumor margin detection (<i>see New route for old cancer agents, page 6</i>).</p> <p><b>SciBX 7(27); doi:10.1038/scibx.2014.791</b>  <b>Published online July 17, 2014</b></p>	Covered by issued and filed patents; available for licensing	<p>Weichert, J.P. <i>et al. Sci. Transl. Med.</i>; published online June 11, 2014;  doi:10.1126/scitranslmed.3007646  <b>Contact:</b> John S. Kuo, University of Wisconsin School of Medicine and Public Health, Madison, Wis.  e-mail:  <a href="mailto:j.kuo@neurosurgery.wisc.edu">j.kuo@neurosurgery.wisc.edu</a>  <b>Contact:</b> Jamey P. Weichert, Collectar Biosciences Inc., Madison, Wis.  e-mail:  <a href="mailto:jweichert@uwhealth.org">jweichert@uwhealth.org</a></p>
Epithelial cancer	Bromodomain containing 4 (BRD4); Wolf-Hirschhorn syndrome candidate 1-like 1 (WHSC1L1; NSD3); NUT midline carcinoma 1 (NUTM1; NUT; C15orf55)	<p>Studies in patient-derived cell cultures and <i>in vitro</i> suggest inhibiting NSD3 could be useful for treating NUT midline carcinoma (NMC). In a patient-derived NMC cell line, RNA sequencing, immunoblotting and siRNA knockdown identified a new NSD3-NUT fusion oncoprotein that prevented cellular differentiation and maintained proliferation. In the cell line, BRD4 inhibition with siRNA or a small molecule induced differentiation and prevented proliferation. In a distinct subset of NMC driven by the known BRD4-NUTM1 fusion protein, NSD3 was required for the formation of nuclear foci enriched with the BRD4-NUTM1 fusion. Next steps include evaluating the oncogenic role of NSD3 in more common forms of cancers and assessing the potential of NSD3 as a therapeutic target.</p> <p><b>SciBX 7(27); doi:10.1038/scibx.2014.792</b>  <b>Published online July 17, 2014</b></p>	Patent application filed; available for licensing	<p>French, C.A. <i>et al. Cancer Discov.</i>; published online May 29, 2014;  doi:10.1158/2159-8290.CD-14-0014  <b>Contact:</b> Christopher A. French, Brigham and Women's Hospital and Harvard Medical School, Boston, Mass.  e-mail:  <a href="mailto:cfrench@partners.org">cfrench@partners.org</a></p>

## This week in therapeutics (continued)

Indication	Target/marker/pathway	Summary	Licensing status	Publication and contact information
Lung cancer	ATG7 autophagy related 7 homolog (ATG7)	<p>Mouse studies suggest acute inhibition of autophagy could be useful for treating lung cancer. In a mouse model of lung cancer, inhibition of autophagy via conditional deletion of <i>Atg7</i> for five weeks decreased tumor volume and burden compared with no alteration. Normal mice with conditional deletion of <i>Atg7</i> lasting more than two months showed susceptibility to infection, neurodegeneration, liver damage and fasting-induced fatal hypoglycemia, suggesting autophagy inhibition might only have a favorable therapeutic profile in acute regimens. Ongoing work includes determining how systemic autophagy deficiency compromises tumor metabolism and growth.</p> <p><b>SciBX 7(27); doi:10.1038/scibx.2014.793</b> Published online July 17, 2014</p>	<p>Covered by issued and filed patents; available for licensing from Rutgers University <b>Contact:</b> Shan Wan, Rutgers University, New Brunswick, N.J. e-mail: <a href="mailto:shanwan@otc.rutgers.edu">shanwan@otc.rutgers.edu</a></p>	<p>Karsli-Uzunbas, G. <i>et al. Cancer Discov</i>; published online May 29, 2014; doi:10.1158/2159-8290.CD-14-0363 <b>Contact:</b> Eileen White, Rutgers University, New Brunswick, N.J. e-mail: <a href="mailto:epwhite@cinj.rutgers.edu">epwhite@cinj.rutgers.edu</a></p>
Prostate cancer	Phosphoinositide 3-kinase (PI3K); poly(ADP-ribose) polymerase (PARP)	<p>Mouse studies suggest a combination of PI3K and PARP inhibitors could be useful for treating hormone-insensitive prostate cancer. In a mouse model of prostate cancer, a combination of PARP and pan-PI3K inhibitors decreased tumor growth and increased survival compared with either compound alone. Next steps could include identifying specific PARP and PI3K isoforms responsible for prostate tumor growth and testing selective inhibitor combinations. PI3K and PARP inhibitors in development to treat prostate cancer include AbbVie Inc.'s PARP inhibitor, veliparib, in Phase I trials; Roche's PI3K inhibitor, RG7422, in Phase I/II trials; and Oncothyreon Inc.'s PI3K inhibitor, PX-866, in Phase I/II testing.</p> <p><b>SciBX 7(27); doi:10.1038/scibx.2014.794</b> Published online July 17, 2014</p>	<p>Patent and licensing status undisclosed</p>	<p>González-Billalabeitia, E. <i>et al. Cancer Discov</i>; published online May 27, 2014; doi:10.1158/2159-8290.CD-13-0230 <b>Contact:</b> Pier Paolo Pandolfi, Harvard Medical School, Boston, Mass. e-mail: <a href="mailto:ppandolf@bidmc.harvard.edu">ppandolf@bidmc.harvard.edu</a></p>
<b>Endocrine/metabolic disease</b>				
Lipodystrophy	Phosphate cytidyltransferase 1 choline- $\alpha$ (PCYT1A)	<p>Biochemical and cell-based studies identified PCYT1A mutants that could be targeted to treat congenital lipodystrophies. Genetic sequencing and analyses of DNA obtained from two patients with similar metabolic disease profiles identified biallelic mutations in <i>PCYT1A</i>. In cell-based biochemical analyses, primary cells expressing mutant <i>PCYT1A</i> mRNA showed lower PCYT1A protein expression and PCYT1A-mediated synthesis of phosphatidylcholine than cells expressing wild-type <i>PCYT1A</i> mRNA. In cultured mouse adipocytes, <i>Pcyt1a</i>-targeting siRNA decreased lipid formation and accumulation compared with scrambled siRNA. Next steps could include testing PCYT1A activity in other forms of metabolic disease and designing compounds to compensate for the enzyme's impaired activity.</p> <p><b>SciBX 7(27); doi:10.1038/scibx.2014.795</b> Published online July 17, 2014</p>	<p>Patent and licensing status unavailable</p>	<p>Payne, F. <i>et al. Proc. Natl. Acad. Sci. USA</i>; published online June 2, 2014; doi:10.1073/pnas.1408523111 <b>Contact:</b> David Savage, University of Cambridge, Cambridge, U.K. e-mail: <a href="mailto:db23@medschl.cam.ac.uk">db23@medschl.cam.ac.uk</a> <b>Contact:</b> Stephen O'Rahilly, same affiliation as above e-mail: <a href="mailto:so104@medschl.cam.ac.uk">so104@medschl.cam.ac.uk</a> <b>Contact:</b> Inês Barroso, Wellcome Trust Sanger Institute, Cambridge, U.K. e-mail: <a href="mailto:ib1@sanger.ac.uk">ib1@sanger.ac.uk</a></p>

## This week in therapeutics (continued)

Indication	Target/marker/pathway	Summary	Licensing status	Publication and contact information
Obesity	Phospholipase A <sub>2</sub> group V (PLA <sub>2</sub> G5); PLA <sub>2</sub> G2E	<p>Mouse studies suggest stabilizing PLA<sub>2</sub>G5 or inhibiting PLA<sub>2</sub>G2E could help treat or prevent metabolic diseases including obesity. In mice fed a high-fat diet, knocking out <i>Pla<sub>2</sub>g5</i> increased weight gain and adipose tissue inflammation compared with no alteration. In mice fed a high-fat diet, <i>Pla<sub>2</sub>g5</i> overexpression in white adipocytes improved insulin control and decreased proinflammatory gene expression. In mice fed a high-fat diet, knocking out <i>Pla<sub>2</sub>g2</i> decreased adipocyte size, fat volume, plasma phospholipids and cholesterol levels compared with no alteration. Next steps include developing specific PLA<sub>2</sub>G5 stabilizers and PLA<sub>2</sub>G2E inhibitors.</p> <p><b>SciBX 7(27); doi:10.1038/scibx.2014.796</b> Published online July 17, 2014</p>	Unpatented; licensing status not applicable	<p>Sato, H. <i>et al. Cell Metab.</i>; published online June 5, 2014; doi:10.1016/j.cmet.2014.05.002  <b>Contact:</b> Makoto Murakami, Tokyo Metropolitan Institute of Medical Science, Tokyo, Japan            e-mail: <a href="mailto:murakami-mk@igakuken.or.jp">murakami-mk@igakuken.or.jp</a></p>
<b>Hematology</b>				
Thalassemia	Family with sequence similarity 132 b (FAM132b); erythroferrone; myonectin)	<p>Mouse studies suggest erythroferrone antagonists could be useful for treating iron overload from blood transfusions for <math>\beta</math>-thalassemia. In a mouse model of <math>\beta</math>-thalassemia, <i>Fam132b</i> knockout decreased hepatic iron accumulation compared with no genetic alteration. Next steps include identifying and testing erythroferrone antagonists in models of <math>\beta</math>-thalassemia and agonists in models of anemia.</p> <p><b>SciBX 7(27); doi:10.1038/scibx.2014.797</b> Published online July 17, 2014</p>	Patent pending; available for licensing	<p>Kautz, L. <i>et al. Nat. Genet.</i>; published online June 1, 2014; doi:10.1038/ng.2996  <b>Contact:</b> Tomas Ganz, University of California, Los Angeles, Calif.            e-mail: <a href="mailto:tganz@mednet.ucla.edu">tganz@mednet.ucla.edu</a></p>
<b>Infectious disease</b>				
Tuberculosis	<i>Mycobacterium tuberculosis</i> decaprenylphosphoryl- $\beta$ -D-ribose 2-oxidase (dprE1)	<p><i>In vitro</i> studies have identified 4-aminoquinolone piperidine amide-based inhibitors of dprE1 that could help treat tuberculosis. <i>In vitro</i>, 4-aminoquinolone piperidine amides were reversible, noncovalent dprE1 inhibitors with IC<sub>50</sub> values under 10 nM. In <i>M. tuberculosis</i> culture, the lead member of the series had a minimum inhibitory concentration of 60 nM. Next steps could include optimizing the lead dprE1 inhibitor and testing it in <i>in vivo</i> models of tuberculosis infection.</p> <p><b>SciBX 7(27); doi:10.1038/scibx.2014.798</b> Published online July 17, 2014</p>	Patent and licensing status unavailable	<p>Naik, M. <i>et al. J. Med. Chem.</i>; published online May 28, 2014; doi:10.1021/jm5005978  <b>Contact:</b> Sandeep R. Ghorpade, AstraZeneca India Pvt. Ltd., Bangalore, India            e-mail: <a href="mailto:sandeepghorpade@hotmail.com">sandeepghorpade@hotmail.com</a>  <b>Contact:</b> Neela Dinesh, same affiliation as above            e-mail: <a href="mailto:neeladin@gmail.com">neeladin@gmail.com</a></p>
<b>Neurology</b>				
Amyotrophic lateral sclerosis (ALS)	Superoxide dismutase 1 (SOD1)	<p>Mouse studies suggest increasing the copper content of the SOD1 metalloprotein could be useful for treating ALS. In a mutant SOD1 mouse model of ALS, daily oral treatment with diacetyl-bis(4-methylthiosemicarbazonato)copper(II) (Cu(II) (at-sm)) improved locomotor function and increased survival compared with vehicle. In spinal cords from these mice, Cu(II)(at-sm) increased the copper content of mutant SOD1 compared with vehicle, suggesting that copper deficiency could underlie the protein's neurotoxicity. Next steps could include developing a screen for compounds that increase SOD1 copper content.</p> <p>At least four companies have compounds that target SOD1 in preclinical development to treat ALS. Procypra Therapeutics LLC has derivatives of Cu(II) (at-sm) in discovery to treat Parkinson's disease (PD).</p> <p><b>SciBX 7(27); doi:10.1038/scibx.2014.799</b> Published online July 17, 2014</p>	Patent and licensing status unavailable	<p>Roberts, B.R. <i>et al. J. Neurosci.</i>; published online June 4, 2014; doi:10.1523/JNEUROSCI.4196-13.2014  <b>Contact:</b> Peter J. Crouch, The University of Melbourne, Melbourne, Victoria, Australia            e-mail: <a href="mailto:pjcrouch@unimelb.edu.au">pjcrouch@unimelb.edu.au</a></p>

## This week in therapeutics (continued)

Indication	Target/marker/pathway	Summary	Licensing status	Publication and contact information
Nerve damage; stroke	Reticulon 4 (RTN4; NOGO-A; NOGO; NOGO-B)	Rat studies suggest treatment with NOGO-A inhibitors followed by physical therapy could help improve motor recovery after stroke. In rats subjected to ipsilateral stroke-induced destruction of the sensory-motor cortex, intrathecal treatment with an anti-Nogo-A antibody for two weeks followed by two weeks of intensive physical training increased motor function recovery compared with anti-Nogo-A antibody treatment given in parallel with physical training or control antibody treatment plus physical training. In the injured rats, the sequential treatment regimen led to the organized growth and sprouting of neuronal fibers, whereas the parallel treatment regimen led to a disorganized growth pattern. Next steps include evaluating the sequential treatment regimen in a Phase I/IIa clinical trial. Novartis AG's anti-NOGO mAb, ATI355, is in Phase I testing to treat spinal cord injury (SCI). GlaxoSmithKline plc's humanized anti-NOGO mAb, ozanezumab, is in Phase II trials to treat amyotrophic lateral sclerosis (ALS). <b>SciBX 7(27); doi:10.1038/scibx.2014.800</b> <b>Published online July 17, 2014</b>	Patented; licensed to Novartis	Wahl, A.S. <i>et al. Science</i> ; published online June 13, 2014; doi:10.1126/science.1253050 <b>Contact:</b> M.E. Schwab, Swiss Federal Institute of Technology Zurich (ETHZ), Zurich, Switzerland e-mail: <a href="mailto:schwab@hifo.uzh.ch">schwab@hifo.uzh.ch</a> <b>Contact:</b> A.S. Wahl, same affiliation as above e-mail: <a href="mailto:wahl@hifo.uzh.ch">wahl@hifo.uzh.ch</a>
Pain	Sphingosine 1-phosphate receptor 1 (S1PR1; S1P1; EDG1)	<i>In vitro</i> and rat studies suggest inhibiting S1PR1 could help treat chemotherapy-induced peripheral neuropathy. In rats treated with paclitaxel, which increases production of the S1PR1 ligand sphingosine 1-phosphate and causes chemotherapy-induced neuropathic pain, intratracheal administration of a selective S1PR1 antagonist decreased mechanical allodynia and hypersensitivity compared with vehicle administration. In rats, oral paclitaxel plus Gilenya fingolimod, a sphingosine 1-phosphate receptor modulator that depletes S1PR1 levels, decreased neuropathic pain compared with vehicle. Next steps include IND-enabling studies on S1PR1 antagonists and agonists. Mitsubishi Tanabe Pharma Corp. and Novartis AG market Gilenya fingolimod to treat multiple sclerosis (MS). Noxxon Pharma AG has the S1PR1 inhibitor NOX-S93 in preclinical testing to treat cancer and autoimmune diseases. <b>SciBX 7(27); doi:10.1038/scibx.2014.801</b> <b>Published online July 17, 2014</b>	Patented by Saint Louis University in the U.S. and patent pending in Europe; exclusively licensed by Biointervene Inc.	Janes, K. <i>et al. J. Biol. Chem.</i> ; published online May 29, 2014; doi:10.1074/jbc.M114.569574 <b>Contact:</b> Daniela Salvemini, Saint Louis University School of Medicine, St. Louis, Mo. e-mail: <a href="mailto:salvemd@slu.edu">salvemd@slu.edu</a>
Schizophrenia	G protein-coupled receptor 52 (GPR52)	<i>In vitro</i> and mouse studies suggest agonizing GPR52 could help treat schizophrenia, which is highly expressed in brain regions associated with disease pathology. Chemical synthesis and testing of benzothioephene-benzamide analogs in human GPR52 <sup>+</sup> hamster cells identified a lead compound that agonized GPR52 at a low nanomolar EC <sub>50</sub> value. In normal mice, the compound showed good pharmacokinetics and brain penetrance. In mice, the compound decreased methamphetamine-induced psychotic behavior compared with vehicle without also causing catalepsy. Next steps could include testing the lead GPR52 agonist in other models of schizophrenia. <b>SciBX 7(27); doi:10.1038/scibx.2014.802</b> <b>Published online July 17, 2014</b>	Patent and licensing status unavailable	Setoh, M. <i>et al. J. Med. Chem.</i> ; published online June 2, 2014; doi:10.1021/jm5002919 <b>Contact:</b> Masaki Setoh, Takeda Pharmaceutical Co. Ltd., Kanagawa, Japan e-mail: <a href="mailto:masaki.setoh@takeda.com">masaki.setoh@takeda.com</a>

## This week in therapeutics (continued)

Indication	Target/marker/ pathway	Summary	Licensing status	Publication and contact information
<b>Ophthalmic disease</b>				
Ophthalmic disease	v-abl Abelson murine leukemia viral oncogene homolog 1 (ABL1); neuropilin 1 (NRP1)	<i>In vitro</i> and mouse studies suggest ABL1 inhibitors could help treat ophthalmic disorders by inhibiting NRP1-mediated angiogenesis. In human endothelial cells, siRNA against NRP1 decreased cell motility, cell spreading and actin remodeling compared with a control siRNA. In a mouse model of oxygen-induced retinopathy, Gleevec imatinib inhibition of Abl1, which forms a complex with Nrp1, decreased pathogenic angiogenesis and vessel formation compared with vehicle treatment. Next steps include testing the effects of Gleevec in additional models of ocular neovascularization. Novartis AG markets Gleevec imatinib to treat various cancers. Roche's Genentech Inc. unit has R7347, an antibody targeting NRP1, in Phase II trials to treat solid tumors.	Patent application filed; available for licensing	Raimondi, C. <i>et al. J. Exp. Med.</i> ; published online May 26, 2014; doi:10.1084/jem.20132330 <b>Contact:</b> Christiana Ruhrberg, University College London, London, U.K. e-mail: <a href="mailto:c.ruhrberg@ucl.ac.uk">c.ruhrberg@ucl.ac.uk</a> <b>Contact:</b> Claudio Raimondi, same affiliation as above e-mail: <a href="mailto:c.raimondi@ucl.ac.uk">c.raimondi@ucl.ac.uk</a>
<b>SciBX 7(27); doi:10.1038/scibx.2014.803 Published online July 17, 2014</b>				
<b>Various</b>				
Colitis; liver cancer	Prostaglandin D <sub>2</sub> (PGD <sub>2</sub> ); PGD <sub>2</sub> receptor (CRTH2; GPR44; CD294)	Mouse studies suggest agonizing the PGD <sub>2</sub> receptor could help treat colitis and prevent colitis-associated colon cancer. In a mouse model of colitis, genetic depletion of the enzyme producing PGD <sub>2</sub> increased colitis severity and tumor formation and decreased survival compared with no alteration. In mice, a PGD <sub>2</sub> receptor agonist decreased colon inflammation and tumor formation compared with no treatment. Next steps include developing new agents to activate PGD <sub>2</sub> signaling.	Unpatented; licensing status not applicable	Iwanaga, K. <i>et al. Cancer Res.</i> ; published online June 1, 2014; doi:10.1158/0008-5472.CAN-13-2792 <b>Contact:</b> Takahisa Murata, The University of Tokyo, Tokyo, Japan e-mail: <a href="mailto:amurata@mail.ecc.u-tokyo.ac.jp">amurata@mail.ecc.u-tokyo.ac.jp</a>
<b>SciBX 7(27); doi:10.1038/scibx.2014.804 Published online July 17, 2014</b>				
Cushing's disease; cardiovascular disease; endocrine/metabolic disease	Hydroxysteroid 11 $\beta$ dehydrogenase 1 (HSD11B1; HSD1)	Mouse studies suggest antagonizing HSD1 could be useful for preventing toxicity caused by glucocorticoid therapy or for treating Cushing's disease. Glucocorticoids are used to treat a variety of inflammatory and metabolic disorders, and patients with Cushing's disease who endogenously overproduce glucocorticoids develop obesity and type 2 diabetes and have increased risk of cardiovascular morbidity. In mice, <i>Hsd1</i> deletion prevented corticosterone-induced elevation of fasting insulin and glucose levels, systolic blood pressure, hepatic triglyceride levels and adiposity. Next steps could include testing HSD1 inhibitors as an adjunct to glucocorticoid therapy in a range of disorders. At least six companies have HSD1 inhibitors in Phase II or earlier testing to treat diabetes or glaucoma.	Patent and licensing status undisclosed	Morgan, S.A. <i>et al. Proc. Natl. Acad. Sci. USA</i> ; published online June 2, 2014; doi:10.1073/pnas.1323681111 <b>Contact:</b> Jeremy W. Tomlinson, University of Birmingham, Birmingham, U.K. e-mail: <a href="mailto:j.w.tomlinson@bham.ac.uk">j.w.tomlinson@bham.ac.uk</a>
<b>SciBX 7(27); doi:10.1038/scibx.2014.805 Published online July 17, 2014</b>				
Inflammatory bowel disease (IBD); graft-versus-host disease (GvHD)	Solute carrier family 2 facilitated glucose transporter member 1 (SLC2A1; GLUT1)	Mouse studies suggest selective inhibition of GLUT1 could help treat IBD and GvHD. In mice, knocking out <i>Glut1</i> in <i>Cd4</i> <sup>+</sup> T cells decreased effector T cell numbers compared with those seen in <i>Glut1</i> <sup>+</sup> controls. In a mouse model of GvHD, adoptive transfer of T cell-depleted bone marrow plus <i>Glut1</i> knockout T cells decreased disease incidence compared with transfer of bone marrow plus <i>Glut1</i> <sup>+</sup> T cells. In a mouse model of IBD, adoptive transfer of <i>Glut1</i> -knockout T cells did not induce inflammation and colitis. Next steps include evaluating GLUT1 inhibitors in inflammatory disorders and elucidating GLUT1 dependencies in other cell types.	Unpatented; licensing status not applicable	Macintyre, A.N. <i>et al. Cell Metab.</i> ; published online June 12, 2014; doi:10.1016/j.cmet.2014.05.004 <b>Contact:</b> Jeffrey C. Rathmell, Duke University, Durham, N.C. e-mail: <a href="mailto:jeff.rathmell@duke.edu">jeff.rathmell@duke.edu</a>
<b>SciBX 7(27); doi:10.1038/scibx.2014.806 Published online July 17, 2014</b>				

## This week in techniques

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

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

Approach	Summary	Licensing status	Publication and contact information
<b>Assays &amp; screens</b>			
<i>In vivo</i> infection system to predict epidemic variants of mosquito-borne RNA viruses	Mosquito and mouse studies suggest deep sequencing of saliva can help predict arbovirus strains that could become epidemic. In <i>Aedes albopictus</i> mosquitoes that carried a pre-epidemic strain of chikungunya virus, deep sequencing of saliva samples was used to detect the emergence of a mutation that results in an epidemic strain. In a prospective analysis of the virus, the epidemic strain acquired two additional mutations. In <i>A. albopictus</i> , the new viral strain had greater infection and dissemination titers than the parental strain. Next steps include applying the method to the chikungunya virus currently spreading in the Caribbean region and adapting the method for use against influenza virus.	Unpatented; licensing status not applicable	Stapleford, K.A. <i>et al. Cell Host Microbe</i> ; published online June 11, 2014; doi:10.1016/j.chom.2014.05.008 <b>Contact:</b> Marco Vignuzzi, Centre National de la Recherche Scientifique (CNRS) UMR 3569, Paris, France e-mail: <a href="mailto:marco.vignuzzi@pasteur.fr">marco.vignuzzi@pasteur.fr</a>
	<b>SciBX 7(27); doi:10.1038/scibx.2014.807</b> Published online July 17, 2014		
<b>Disease models</b>			
Macrophage model of Gaucher's disease	A macrophage model of Gaucher's disease could help identify new therapies to treat the condition, which is caused by a genetic deficiency in glucocerebrosidase (GBA; GCase). Induced pluripotent stem (iPS) cells and monocytes derived from patients with Gaucher's disease or healthy subjects were used to generate macrophages. Patient-derived macrophages showed impaired bacteria-induced reactive oxygen species production, decreased GBA activity and increased lysosomal storage of GBA substrates compared with macrophages generated from healthy subjects. In the patient-derived macrophages, a chaperone protein that restores mutant GBA folding increased GBA activity with potency comparable to that of recombinant GBA. Next steps could include developing screening assays that use the macrophages to identify new therapeutic candidates.	Patent and licensing status unavailable	Aflaki, E. <i>et al. Sci. Transl. Med.</i> ; published online June 11, 2014; doi:10.1126/scitranslmed.3008659 <b>Contact:</b> Ellen Sidransky, National Institutes of Health, Bethesda, Md. e-mail: <a href="mailto:sidranse@mail.nih.gov">sidranse@mail.nih.gov</a>
	<b>SciBX 7(27); doi:10.1038/scibx.2014.808</b> Published online July 17, 2014		
<b>Drug platforms</b>			
Chemically defined medium for generation of human cardiomyocytes from induced pluripotent stem (iPS) cells	A chemically defined medium for differentiating human iPS cells into cardiomyocytes could be useful for generating cell-replacement therapies for cardiac repair. The culture medium consists of RPMI 1640, L-ascorbic acid 2-phosphate and rice-derived recombinant human albumin. The medium was able to generate sheets of cardiomyocytes with a yield of up to 100 cardiomyocytes per human iPS cell. The resulting human cardiomyocytes were not fully differentiated but still showed cardiomyocyte-like electrophysiological behaviors and expressed multiple cardiomyocyte markers. Next steps could include optimizing the culture medium and associated protocols to further mature the cardiomyocytes.	Patent and licensing status unavailable	Burridge, P.W. <i>et al. Nat. Methods</i> ; published online June 15, 2014; doi:10.1038/nmeth.2999 <b>Contact:</b> Joseph C. Wu, Stanford University School of Medicine, Stanford, Calif. e-mail: <a href="mailto:joewu@stanford.edu">joewu@stanford.edu</a> <b>Contact:</b> Paul W. Burridge, same affiliation as above e-mail: <a href="mailto:burridge@stanford.edu">burridge@stanford.edu</a>
	<b>SciBX 7(27); doi:10.1038/scibx.2014.809</b> Published online July 17, 2014		
Depletion of host hematopoietic stem cells (HSCs) <i>in utero</i> improves engraftment after liver mononuclear cell transplant in fetuses	Mouse studies suggest <i>in utero</i> depletion of HSCs can improve engraftment after liver mononuclear cell transplant. In fetal mice, a mouse anti-stem cell factor receptor tyrosine kinase (c-Kit; Kit; Cd117) antibody was shown to deplete HSCs. In fetal mice, depletion of HSCs with the mouse antibody prior to congenic liver mononuclear cell transplantation increased the rate and level of donor cell engraftment compared with no depletion. Next steps include using a humanized version of the antibody in <i>in utero</i> nonhuman primate bone marrow transplant models of hemoglobinopathies, such as thalassemia or sickle cell disease.	Patent and licensing status unavailable	Derderian, S.C. <i>et al. Blood</i> ; published online May 30, 2014; doi:10.1182/blood-2014-02-550327 <b>Contact:</b> Tippi C. MacKenzie, University of California, San Francisco, Calif. e-mail: <a href="mailto:tippi.mackenzie@ucsfmedctr.org">tippi.mackenzie@ucsfmedctr.org</a>
	<b>SciBX 7(27); doi:10.1038/scibx.2014.810</b> Published online July 17, 2014		

## This week in techniques (continued)

Approach	Summary	Licensing status	Publication and contact information
Influenza A virus hemagglutinin stem fragment to induce broadly neutralizing antibodies	<i>In vitro</i> and mouse studies suggest the influenza A virus hemagglutinin stem fragment could help protect against influenza virus infection. The fragment contained an isoleucine zipper that produced H1HA10-Foldon, a trimeric hemagglutinin stem immunogen that harbors about 95% of the epitope bound by the broadly neutralizing antibody CR6261. In binding assays, sera obtained from mice immunized with H1HA10-Foldon neutralized five different strains of influenza virus, whereas sera from mice immunized with an inactivated virus did not. In mice, prophylactic immunization with H1HA10-Foldon protected against lethal challenge with influenza virus. Next steps include testing the immunogen with other adjuvants and immunization regimes in mice and ferrets. Johnson & Johnson's Crucell N.V. unit has the hemagglutinin-targeting, broadly neutralizing antibody CR6261 in Phase I trials to treat influenza.	Patent application filed; available for licensing from the Indian Institute of Science	Mallajosyula, V.V.A. <i>et al. Proc. Natl. Acad. Sci. USA</i> ; published online June 9, 2014; doi:10.1073/pnas.1402766111 <b>Contact:</b> Raghavan Varadarajan, Indian Institute of Science, Bangalore, India e-mail: <a href="mailto:varadar@mbu.iisc.ernet.in">varadar@mbu.iisc.ernet.in</a> <b>Contact:</b> Xiaoping Liang, Merck Research Laboratories, West Point, Pa. e-mail: <a href="mailto:liangxiaoping@walvax.com">liangxiaoping@walvax.com</a>
<b>SciBX 7(27); doi:10.1038/scibx.2014.811</b> Published online July 17, 2014			
<b>Imaging</b>			
Luciferase-based indicators of drugs (LUCIDs) for point-of-care monitoring	A luciferase-based assay could be used to quickly and quantitatively assess drug concentrations in patient samples. LUCIDs have three components: a receptor protein that binds the drug of interest, a luciferase and a synthetic molecule containing a fluorophore that is coupled to a ligand that also binds the receptor. The drug concentration can be calculated using the ratio of the luciferase signal to the fluorophore signal, which is enhanced when the ligand binds the receptor and is reduced when the drug displaces the ligand. In patient sera samples, individual LUCIDs designed to detect six different drugs quantified drug levels based on titrated emission data collected with a digital camera. Next steps include developing test strips and a handheld reader device to assess drug concentrations from a drop of blood.	Patent application filed covering the LUCID technology; unavailable for licensing	Griss, R. <i>et al. Nat. Chem. Biol.</i> ; published online June 8, 2014; doi:10.1038/nchembio.1554 <b>Contact:</b> Kai Johnsson, Swiss Federal Institute of Technology Lausanne, Lausanne, Switzerland e-mail: <a href="mailto:kai.johnsson@epfl.ch">kai.johnsson@epfl.ch</a>
<b>SciBX 7(27); doi:10.1038/scibx.2014.812</b> Published online July 17, 2014			
Ultra-small rigid platform (USRP) contrast agents for MRI detection of non-small cell lung cancer (NSCLC)	Mouse studies suggest orotracheal delivery of USRP contrast agents for MRI could help noninvasively diagnose NSCLC. In an orthotopic mouse model of bioluminescent NSCLC, USRP contrast agents delivered via orotracheal or i.v. routes accumulated in tumors and colocalized with the bioluminescent signal. In the mice, orotracheal delivery of the USRP contrast agent resulted in a higher MRI signal-to-noise ratio and contrast-to-noise ratio than i.v. delivery of a marketed contrast agent. Next steps could include evaluating the contrast agents in additional animal tumor models.	Patent and licensing status unavailable	Bianchi, A. <i>et al. Proc. Natl. Acad. Sci. USA</i> ; published online June 9, 2014; doi:10.1073/pnas.1402196111 <b>Contact:</b> Yannick Crémillieux, University of Bordeaux Segalen, Bordeaux, France e-mail: <a href="mailto:yannick.cremillieux@ubordeaux2.fr">yannick.cremillieux@ubordeaux2.fr</a>
<b>SciBX 7(27); doi:10.1038/scibx.2014.813</b> Published online July 17, 2014			
<b>Markers</b>			
Monitoring microRNA-1202 (miR-1202) expression to predict antidepressant treatment response	Cell culture and patient sample studies suggest monitoring miR-1202 expression could help predict response to antidepressants in patients with depression. In human prefrontal cortex samples, miR-1202 levels were lower in patients with depression than healthy controls. In human neural progenitor cells, chronic treatment with the marketed antidepressants imipramine or Celexa citalopram increased miR-1202 levels compared with no treatment. In blood samples from patients with depression, miR-1202 expression was lower in remitter patients than nonresponders and controls, and miR-1202 levels were higher in patients after Celexa treatment than before treatment. Next steps could include testing correlations of miR-1202 with other antidepressants and in wider patient populations. Imipramine is a generic tricyclic antidepressant. Citalopram is a generic selective serotonin reuptake inhibitor and is marketed by H. Lundbeck A/S and Actavis plc as Celexa.	Patent and licensing status unavailable	Lopez, J.P. <i>et al. Nat. Med.</i> ; published online June 8, 2014; doi:10.1038/nm.3582 <b>Contact:</b> Gustavo Turecki, McGill University, Montreal, Quebec, Canada e-mail: <a href="mailto:gustavo.turecki@mcgill.ca">gustavo.turecki@mcgill.ca</a>
<b>SciBX 7(27); doi:10.1038/scibx.2014.814</b> Published online July 17, 2014			

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Runt-related transcription factor 1	10	STAT3	12	<b>U</b>		<b>W</b>	
RUNX1	10	STAT5	4	Ubiquitin specific peptidase 30	1	WHSC1L1	12
<b>S</b>		Stem cell factor receptor tyrosine kinase	17	UDP glucuronosyltransferase 1 family polypeptide A1	8	Wolf-Hirschhorn syndrome candidate 1-like 1	12
S1P1	15			UDP glucuronosyltransferase	8	<b>Y</b>	
S1PR1	15			UGT1A1	8	Yervoy	12
Serotonin	18						