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Browning fat

By *Joanne Kotz, Senior Editor*

Dana-Farber Cancer Institute researchers have identified a new hormone dubbed irisin that is induced by exercise and triggers the conversion of white fat to brown-like fat in mice, leading to increased energy expenditure.¹ **Ember Therapeutics Inc.** has licensed the findings and is generating stabilized versions of irisin in preparation for clinical trials in obesity and type 2 diabetes.

In a separate study, **Harvard University** researchers have developed a method for converting human pluripotent stem cells into white and brown adipocytes.² The Harvard team is collaborating with **Roche** to use the cell lines for multiple screens, including looking for molecules that promote brown-like phenotypes in white adipocytes.

There are two types of fat—white and brown. White adipose tissue (WAT) stores energy as triglycerides, whereas brown adipose tissue (BAT) metabolizes triglycerides to generate heat. The mobilization of triglycerides by BAT helps control weight and overall metabolic status.

BAT was long known to exist in rodents and human infants, but it was not until 2009 that a trio of papers in *The New England Journal of Medicine* identified BAT in human adults.³⁻⁵

The hope is that molecules that activate brown fat or induce the conversion of white fat to brown-like fat could help treat metabolic diseases such as obesity and diabetes.

Muscling in

A team led by Bruce Spiegelman, professor in the Department of Cell Biology at Dana-Farber, was intrigued by the previous observation that transgenic mice with increased levels of peroxisome proliferation-activated receptor- γ coactivator 1 α (Ppargc1 α ; Pgc-1 α) in muscle were resistant to age-related obesity and diabetes.⁶ PGC-1 α is induced in muscle by exercise.

Spiegelman's team hypothesized that exercise-induced PGC-1 α might be stimulating the secretion of factors from muscle that have beneficial effects on tissues involved in regulating metabolism.

The team first looked for a protein that was upregulated in response to PGC-1 α expression and identified the membrane protein fibronectin type III domain containing 5 (FNDC5) as a potential transcriptional target of PGC-1 α .

The next question was whether FNDC5 could be secreted. When FNDC5 was expressed in cells, it was proteolytically cleaved to release a shorter, previously uncharacterized variant that Spiegelman's team named irisin. Strikingly, the amino acid sequence of irisin is identical in mice and humans.



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The team then looked to see if irisin levels were regulated by exercise. Indeed, exercise increased irisin levels in the blood of both mice and humans.

In mice with adenoviral vector-mediated overexpression of Fndc5, levels of irisin in the blood were threefold higher than those in mice with normal expression of Fndc5. These animals also had greater amounts of brown-like fat in their subcutaneous white fat pad than controls.

Together, the results suggest a pathway in which exercise induces irisin secretion, leading to the browning of white fat (see Figure 1, “Exercise messenger”).

Finally, the team asked whether irisin had therapeutic benefits.

When fed a high fat diet, mice overexpressing Fndc5 had less weight gain, better glucose tolerance and lower fasting insulin levels than mice with normal Fndc5 expression.

Results were published in *Nature*.

“Irisin certainly has appeal as a factor that is secreted in response to exercise and appears to be capable of inducing changes in fat metabolism and glycemic control in mice,” said Thomas Hughes, president and CEO of Zafgen Inc.

Zafgen’s ZGN-433 has completed Phase Ib testing in obesity. The compound inhibits methionine aminopeptidase 2 (MetAP2) and modulates the metabolic regulation of fat storage and breakdown.

According to Hughes, irisin’s therapeutic utility in humans is an open question awaiting clinical testing. “The authors speculate that

“Irisin certainly has appeal as a factor that is secreted in response to exercise and appears to be capable of inducing changes in fat metabolism and glycemic control in mice.”

— Thomas Hughes, Zafgen Inc.

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Figure 1. Exercise messenger. Dana-Farber Cancer Institute researchers have identified a new hormone, irisin, which mediates some of the benefits exercise has on metabolism.

Exercise induces increased expression of peroxisome proliferation-activated receptor- γ coactivator 1 α (PPARGC1A; PGC-1 α) [a], which boosts expression of the membrane protein fibronectin type III domain containing 5 (FNDC5) [b]. FNDC5 is proteolytically cleaved, resulting in the release of irisin [c], which is carried in the blood to white adipose tissue [d], where it stimulates the browning of white fat [e].

In mice fed a high-fat diet, greater expression of irisin decreased weight gain and increased glucose tolerance compared with normal irisin expression.

the protein may exert its effects through induction of PPAR α . PPAR α stimulation has been seen to reduce body weight in laboratory animals but so far has not translated into body weight changes or improvements in glycemic control in humans," he noted.

Spiegelman responded that "irisin does many things, only one of which is to regulate PPAR α in adipose cells." He added that, in contrast to irisin, activators of peroxisome proliferation-activated receptor- α (PPARA; PPAR α) have never been shown to induce the browning of white fat.

Ember gets stoked

Ember, which was cofounded by Spiegelman and holds exclusive rights to the irisin technology from Dana-Farber, plans to put a variant of the hormone into the clinic in 2014 for obesity and type 2 diabetes.

Lou Tartaglia, Ember's president and interim CEO, said the company has produced stabilized versions of irisin. He added that in mice, the variants produced browning of white fat and metabolic improvements.

The company also is pursuing alternative targets for inducing the browning of white fat or for activating brown fat. Tartaglia said Ember is running target-based *in vitro* screens and pathway-oriented cellular screens on a number of targets that have been identified by the company's founders and scientific advisory board members, including bone morphogenetic protein 7 (BMP7; OP-1) and PR domain containing 16 (PRDM16).

Spiegelman's laboratory is now focused on identifying irisin's receptor.

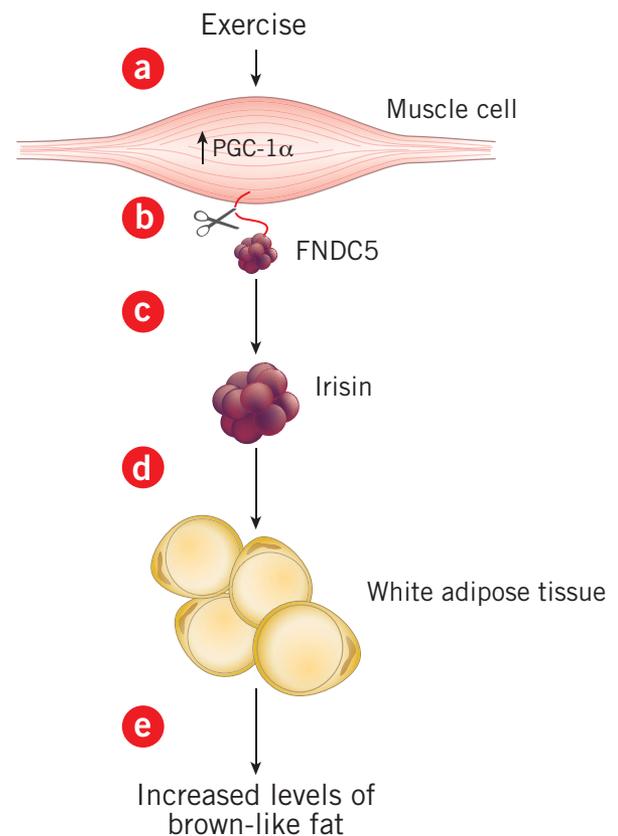
Dana-Farber has filed a patent application covering the results reported in *Nature*.

Fat models

One promising outcome of Spiegelman's study was that the hormone characterized first in mice, irisin, was subsequently shown to be activated by exercise in people. Historically, not all studies of metabolism in mice and in mouse adipocytes have directly translated to humans.

"Mice don't get heart attacks. Many mice are hard to make fat. They don't have the same metabolic problems as humans," said Chad Cowan, an assistant professor in the Department of Stem Cell and Regenerative Biology at Harvard and a principal faculty member at the **Harvard Stem Cell Institute**.

On the flip side, human cell culture work has required immortalized



cell lines because human WAT is not easily cultured. Cowan added that "there has been very limited access to human brown fat."

To develop a better model system, a team led by Cowan turned to human pluripotent stem cells. The group first converted human induced pluripotent stem (iPS) cell lines and human embryonic stem cell (hESC) lines into mesenchymal progenitor cells. Transducing these progenitor cells with PPAR γ (PPAR γ) led to the formation of white adipocytes. Transduction with PPAR γ in combination with CCAAT enhancer binding protein- β (CEBPB; CRP2) and PRDM16 generated brown adipocytes.

The response of the white adipocytes to insulin was modulated with known physiological regulators, suggesting the cells can model insulin sensitivity and resistance. The brown adipocytes had the expected increased level of mitochondrial activity, suggesting they are a functional model for brown fat.

Subcutaneous implantation of the adipocytes in mice led to the formation of BAT and WAT. Results were published in *Nature Cell Biology*.

Cowan's team is collaborating with Roche to use the human adipocyte cell lines for drug discovery. Under a 2010 deal between Roche, Harvard University and **Massachusetts General Hospital**, the pharma is using stem cell lines developed by academics for drug screening in cardiovascular and metabolic diseases.

"The possibility to culture human brown and white adipose cells allows us to assess the efficacy of novel drug candidates in a highly relevant human cell system," said Kurt Amrein, scientific expert in metabolism at Roche.

The pharma is using Cowan's adipocyte cell lines for three types of screens.

First, Roche is "establishing human white adipocytes from iPS cells isolated from subjects with metabolic disorders. Cells with a clear deficit will be used in phenotypic screens aimed at normalizing function," said Amrein.

The company is also setting up two screens focusing on brown fat. "We have a keen interest in identifying either small molecules that are able to convert white into brown-like adipocytes or identifying molecules that promote increased brown adipocyte formation from precursor cells," he said.

Hughes said the feasibility and therapeutic outcome of activating brown fat in humans are unknown. "Brown fat serves a primary purpose of heating the blood as an adaptive response to cold exposure. Obese individuals may or may not tolerate increased heat production for long periods of time," he said. "Secondly, brown fat function may need to be stimulated under physiological conditions—this stimulation is normally driven by sympathetic nerves—through adrenaline—and thyroid hormone. This stimulus may be needed to yield the benefits of brown fat induction. If multiple stimuli are needed, or true cold exposure is necessary, these limitations might impact the usefulness of a therapy."

Amrein acknowledged that "the exact role BAT plays in obesity and the metabolic syndrome is still a matter of debate. However, many recent reports indicate that it may play a major role and may offer a completely new therapeutic target for metabolic diseases."

Tartaglia, who also is a partner at **Third Rock Ventures**, told *SciBX* that Ember has studied the mice generated by Spiegelman in which transgenic expression of *Prmd16* leads to browning of white fat.⁷ "We've looked for things that were potentially concerning like increases in body temperature and haven't found anything. However, until we do very thorough toxicology—especially in nonhuman primates and people—we really won't know for sure," he said.

Massachusetts General Hospital, where Cowan initiated the research, has filed a patent application covering the methods reported in *Nature Cell Biology*. Roche has a nonexclusive license, and the technology is available for additional licensing from **Partners HealthCare** Research Ventures & Licensing.

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COMPANIES AND INSTITUTIONS MENTIONED

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Harvard University, Cambridge, Mass.
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Partners HealthCare, Boston, Mass.
Roche (SIX:ROG; OTCQX:RHHBY), Basel, Switzerland
Third Rock Ventures, Boston, Mass.
Zafgen Inc., Cambridge, Mass.

Closing the gap on liver toxicity

By **Tim Fulmer**, Senior Writer

U.S. researchers have identified a small molecule gap junction inhibitor that protects mice from drug-induced liver toxicity.¹ The team has founded **Heptotech Inc.** to further characterize and optimize the inhibitor.

Gap junctions are multiprotein channel structures that directly connect the cytoplasm of two adjacent cells, allowing for electrical and chemical communication.

In previous cell culture studies, Martin Yarmush and colleagues showed that gap junctions play a role in the propagation of inflammatory and antiviral signals between several cell types including hepatocytes.² Yarmush is professor of surgery at **Harvard Medical School** and **Massachusetts General Hospital**.

The pathogenesis of drug-induced liver injury (DILI) involves proinflammatory cellular damage propagating from an initial injury site to an increasingly larger area of the liver.³ DILI is most commonly caused by an overdose of the analgesic acetaminophen, and the only drug approved to counteract that process is N-acetylcysteine (NAC).

NAC is most effective when given within eight hours of an acetaminophen overdose. Standard treatment durations are 72 and 48 hours for the oral and i.v. formulations, respectively.⁴

Yarmush and colleagues hypothesized that selectively blocking gap junctions in the liver might help limit DILI or at least slow its progression.

To test that hypothesis, the researchers generated mice deficient in gap junction protein β_1 , 32 kDa (Gjb1; Cx32; connexin-32), the main gap junction protein in the liver, and treated them with a hepatotoxin called thioacetamide that is known to cause liver failure.

The Cx32 knockout mice receiving thioacetamide had less liver damage and a lower hepatic inflammatory response than wild-type mice given the same toxin. In the knockout mice, liver tissue showed less recruitment of neutrophils and lower levels of multiple proinflammatory cytokines including tumor necrosis factor- α (Tnf- α), Il-6 and chemokine CC motif ligand 5 (Rantes; Ccl5).

Moreover, all knockout mice survived a lethal dose of the toxin, whereas all wild-type mice died.

Next, the researchers used cell-based assays to screen libraries for small molecule inhibitors of CX32. The top hit was the small molecule 2-aminoethoxydiphenyl borate (2APB), a research tool previously shown to transiently bind and inhibit CX32 gap junctions *in vitro*.⁵

To test whether 2APB also decreases DILI *in vivo*, the team turned to mouse models of thioacetamide- and acetaminophen-induced liver injury. Indeed, 2APB given 1.5 hours after chemical challenge reduced hepatotoxicity compared with vehicle control, as measured by serum liver enzymes and liver histology.

2APB also lowered serum liver enzyme levels and limited further hepatocellular damage and necrosis compared with vehicle when given six hours after chemical challenge, which is after the onset of hepatic necrosis.

Data were published in *Nature Biotechnology*.

The authors wrote that 2APB and similarly acting compounds “may provide a clinically useful means to treat liver injury associated with dose-dependent hepatotoxic drugs such as acetaminophen.”

“The strengths of this study are that it uses two models of DILI—thioacetamide and acetaminophen—thus supporting the idea that a number of investigators have been building upon that innate immune activation is a feature common to many forms of hepatocyte death and thus common to many agents that cause DILI,” said Wajahat Mehal, associate professor of medicine at **Yale University**.

In 2009, Mehal and colleagues published data on mouse models of DILI showing that DNA released from dying hepatocytes activates the innate immune response via toll-like receptor 9 (Tlr9) and the NLR family pyrin domain containing 3 (Nlrp3; Nalp3) inflammasome.⁶

“The advantage of a CX32 inhibitor is that it acts at a later stage in the acetaminophen hepatotoxicity process than N-acetylcysteine”

and thus could have a wider therapeutic window, said Mehal.

“It will be important to look at the potential effects of 2APB on other connexin proteins as well as consider the proper length of treatment to achieve the optimal therapeutic effect.”

—**Anthony Phillips**,
CoDa Therapeutics Inc.

Minding the gap

Going forward, Mehal wanted to see the gap junction inhibitor tested in additional animal models of acetaminophen-induced liver toxicity.

Andrew Harris, professor of pharmacology and physiology at the **UMDNJ New Jersey Medical School**, said it will be important to see whether 2APB has any effects in tissues outside the liver, because gap junction proteins are expressed throughout the body. For example, the proteins are essential for proper cardiac function.

In 2007, Harris published research showing that 2APB inhibited CX32 and gap junction protein β_2 , 26 kDa (GJB2; connexin-26; CX26), a gap junction protein expressed in the liver and other tissues.⁴

Those data “raise some questions about the specificity of 2APB,” said Anthony Phillips, medical director of **CoDa Therapeutics Inc.** “It will be important to look at the potential effects of 2APB on other connexin proteins as well as consider the proper length of treatment to achieve the optimal therapeutic effect.”

CoDa has two compounds in development that target gap junction proteins. Lead molecule Nexagon is a topically delivered oligonucleotide that targets gap junction protein α_1 , 43 kDa (GJA1; CX43; connexin-43). The compound is in Phase II testing to treat chronic venous leg ulcers. The company also has a peptide mimetic that targets gap junction proteins in preclinical development for undisclosed indications.

CoDa cofounder David Becker told *SciBX* that “to the best of our knowledge, there are no small molecules that are totally specific for a particular gap junction protein. That’s a key reason why CoDa went the antisense route to downregulate the expression of a specific connexin without any off-target effects.”

(Continues on p. 6)

Tapping into TASP1

By Kai-Jye Lou, Staff Writer

Researchers from **Washington University in St. Louis** and colleagues from other U.S. institutions have identified a potent small molecule inhibitor of *taspase-1*.¹ The group now plans to use the small molecule as a scaffold to design drug-like inhibitors of the cancer-associated enzyme.

Taspase-1 (TASP1) is a protease linked to proliferation and apoptosis in multiple cancer types including glioblastoma and melanoma.^{2,3}

Previously, James Hsieh and collaborators at **Stanford University** used the structural data of the TASP1 active site to help rationally design peptide-based inhibitors.⁴ However, the resulting compounds lacked potency and were unlikely to be useful *in vivo* because TASP1 acts on intracellular targets.

At the time, Hsieh was an assistant professor of medicine at Washington University in St. Louis. He is now a laboratory head in the human oncology and pathogenesis program at **Memorial Sloan-Kettering Cancer Center**.

Hsieh and collaborators have now switched gears and used a cell-based, dual-fluorescence functional assay to screen a library of synthetic compounds from the **National Cancer Institute** (NCI) for molecules that target TASP1. The best hit was the arsenic acid compound NSC48300, which inhibited TASP1 with an IC_{50} of about 7.5 μ M.

NSC48300 did not compete with any substrates of TASP1, indicating that the compound is allosterically inhibiting the enzyme's activity. Thus, the data suggest the possibility of developing TASP1 inhibitors that do not target the enzyme's active site.

In mouse models of TASP1-overexpressing human breast cancer and glioma, NSC48300 decreased tumor growth compared with vehicle.

Results were published in *Cancer Research*.

“This series of preclinical studies has demonstrated the feasibility of targeting *taspase-1* to treat cancer.”

—James Hsieh,
Memorial Sloan-Kettering
Cancer Center

The team included researchers from the Washington University in St. Louis, Memorial Sloan-Kettering, the **Rosalind Franklin University of Medicine and Science**, the **Dana-Farber Cancer Institute** and NCI. Hsieh carried out the study while at Washington University in St. Louis.

Gearing up for drug discovery

Although NSC48300 is a clear step in the right direction, the compound itself is unlikely to advance into the clinic.

“This series of preclinical studies has demonstrated the feasibility of targeting *taspase-1* to treat cancer,” Hsieh told *SciBX*. “Although the short-term use of NSC48300 in mice is relatively safe, the fact that NSC48300 is an arsenic acid-containing compound is expected to have undesirable toxicities upon long-term use. It provides a scaffold and serves as a tool in the discovery of actual therapeutic compounds.”

Enrique Zudaire Ubani noted that NSC48300 is a promiscuous compound that can affect a broad range of molecular targets. Zudaire Ubani is a staff scientist at the Angiogenesis Core Facility at NCI and a co-inventor on a patent application describing NSC48300 as an antiangiogenic small molecule.

Thus, Hsieh said the group's future work with TASP1 will focus on four areas.

“First, we are working with the Chemical Biology Consortium through NCI to develop more potent, more specific and less toxic compounds than NSC48300. Second, we would like to identify the most appropriate types of cancers to treat. Third, we would like to develop a probe that can be easily utilized to examine the *in vivo* activity of *taspase-1* and the efficacy of *taspase-1* inhibitors. And fourth, we need to understand whether *taspase-1* inhibitors can synergize with other anticancer drugs,” he said.

In addition, Hsieh noted that the group is working with collaborators at **Columbia University** to cocrystallize NSC48300 and TASP1 to better understand the compound's mechanism of action.

(Continues on p. 7)

(Continued from “Closing the gap on liver toxicity,” p. 5)

Becker is a professor of cellular imaging at the **University College London**.

The findings in the paper are covered by patents licensed to Heprotech, a company founded by corresponding author Yarmush and lead author Suraj Patel, who is a research fellow in the Massachusetts General Hospital Department of Surgery.

Next steps for the company include studying any off-target effects of gap junction inhibitors and understanding the long-term effects of blocking liver-specific gap junction channels, said Yarmush. He declined to provide additional details.

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COMPANIES AND INSTITUTIONS MENTIONED

CoDa Therapeutics Inc., San Diego, Calif.

Harvard Medical School, Boston, Mass.

Heprotech Inc., Boston, Mass.

Massachusetts General Hospital, Boston, Mass.

UMDNJ New Jersey Medical School, Newark, New Jersey

University College London, London, U.K.

Yale University, New Haven, Conn.

Roland Stauber, professor of molecular and cellular oncology at the **Johannes Gutenberg University Mainz**, said that “characterizing the active form of *taspase-1 in vivo* will be important for the rational design of strong *taspase-1* inhibitors.”

Stauber and colleagues developed the first cell-based assays to dissect the function of TASP1 and also used them to identify two small molecules that partially inhibited the enzyme’s activity.^{5,6}

He went on to point out that the existing crystal structure for TASP1 (ref. 7) might not accurately mirror the form of the protease that should be targeted for therapeutic applications. Indeed, he thinks the rational design of potent TASP1 inhibitors has been challenging in part because the structure of the active protease *in vivo* is still unclear.

Stauber also wanted to see additional studies directly linking TASP1 to various types of cancer, including breast and brain cancer, as well as additional *in vivo* data showing that NSC48300 is indeed a specific TASP1 inhibitor.

Washington University in St. Louis has filed a patent application covering TASP1 inhibitors and their uses. The work is available for licensing.

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COMPANIES AND INSTITUTIONS MENTIONED

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National Cancer Institute, Frederick, Md.
Rosalind Franklin University of Medicine and Science, Chicago, Ill.
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2-HG on the brain (tumor)

By Michael J. Haas, Senior Writer

A **Harvard Medical School** team has shown that a specialized MRI technique can noninvasively diagnose patients with isocitrate dehydrogenase 1-mutant gliomas by detecting a key metabolite produced by the tumors.¹ Although few imaging centers have the resources needed to adopt the method for routine diagnostic applications, **Agios Pharmaceuticals Inc.** plans to use it to study the biology of the isocitrate dehydrogenase 1-mutant gliomas and monitor the response to glioma therapies the company has in preclinical development.

In normal tissues, isocitrate dehydrogenase 1 (IDH1) plays a role in glucose metabolism by catalyzing the conversion of isocitrate to α -ketoglutarate. IDH1 and a related enzyme, IDH2, are mutated in about 70% of brain cancers and 25% of adult leukemias.² The mutated enzymes also occur in a smaller percentage of other solid tumors. The current method of diagnosing IDH1-mutant glioma requires a biopsy.

In 2009, Agios showed that expression of the mutant IDH1 enzyme resulted in higher levels of the metabolite (*R*)-2-hydroxyglutarate (2-HG) than wild-type IDH1 expression in tumors and normal brain tissue.³ The study did not elucidate the metabolite's role in tumor growth and progression but did suggest 2-HG could be a marker for IDH1-mutant gliomas.⁴

In the new study, the team postulated that magnetic resonance spectroscopy (MRS) could detect 2-HG in the brain to diagnose IDH1-mutant gliomas noninvasively. The problem was that standard 1D MRS techniques generated signals from other abundant brain metabolites—primarily glutamate and glutamine—that overlapped with signals from 2-HG. Thus, it was difficult to detect and quantify 2-HG *in vivo*.

To overcome the problem, the team turned to a 2D MRS technique that is more complex and time-consuming than standard 1D MRS. Indeed, the 2D technique produced 2-HG signals that were readily distinguished from those of other metabolites.

2D MRS exposes a sample to two series of frequencies and then displays the results for each on a different axis to form a 2D plot. By examining how and where the two sets of results overlap, the spectroscopist can assign each signal to a particular proton—and thus the molecule to which it belongs—with greater confidence than when using 1D MRS.

The team used the 2D MRS technique on patient biopsies from gliomas expressing mutant or wild-type IDH1 to refine the method for the quantification of 2-HG. Finally, the team used the method on six patients with glioma and four healthy controls and correctly diagnosed each as having a mutant IDH1 glioma, wild-type IDH1 glioma or no glioma.

The group included researchers from **Massachusetts General Hospital, Dana-Farber Cancer Institute, Massachusetts Institute of**

Technology and Agios. Data were reported in *Science Translational Medicine*.¹

“The key advantage of the team’s method is that it is noninvasive,” Agios CSO Scott Biller told *SciBX*. “2-HG has not been detected in the blood plasma of patients with IDH1-mutant gliomas, and the question of whether it appears in urine or cerebrospinal fluid has not been thoroughly explored. Currently, there is no other noninvasive way to use 2-HG as a marker to diagnose those gliomas.”

Noninvasive diagnosis could be useful when a standard biopsy is not feasible, he said. Additionally, Biller said the method “could be used over time to follow the effects of drug treatment on IDH1-mutant gliomas when surgery isn’t possible or to watch for tumor recurrence” after surgery.

Patrick Wen added that the method might obviate the need for an invasive biopsy in cases in which “the patient presents with a lesion in the brain that is not necessarily a glioma but could be brain inflammation or scarring that results from another cause.” If the lesion is relatively small or the physician

suspects that it is not a tumor, a negative result from the team’s method could help confirm a noncancer diagnosis, he said.

Wen is director of neuro-oncology at Dana-Farber and professor of neurology at Harvard Medical School. He was not involved in the study.

New dimensions in imaging

Wen cautioned that the method is unlikely to find routine clinical use in the near term, given the complexity of the 2D MRS technique and the need to validate the findings in a larger patient population.

Because MRS diagnostics are usually not reimbursed by healthcare payers, “most imaging facilities do not have the equipment, expertise and time necessary to conduct the lengthy experiments” described in the study, said Wen.

“If future studies validate the method and 2-HG as a marker, then people might pay more attention to 2D MRS and put more resources into it,” added Wen. Until then, he said, clinical use of the method would probably be confined to large, specialized imaging centers.

In the meantime, Wen said the method could be used to test whether therapies targeting IDH1-mutant tumors decrease 2-HG levels in animal models. “This could provide preclinical proof of concept that the method could monitor tumor response in patients,” he said.

Indeed, Agios plans to incorporate the method into the preclinical development of therapies to treat IDH1-mutant gliomas. Agios has compounds targeting IDH1 and IDH2 in preclinical development to treat brain cancer, acute myelogenous leukemia (AML) and other cancers in which mutant IDH1 or IDH2 occurs.

“We have already made great progress in understanding the connection between mutant IDH1, 2-HG and gliomal tumors,” said Biller. “As we learn more about the role of 2-HG in gliomal biology, we will apply the method to our studies in animal models.”

He added that Agios plans to validate 2D MRS detection of 2-HG as a marker of response to treatment in IDH1-mutant glioma in animal

“If future studies validate the method and 2-HG as a marker, then people might pay more attention to 2D MRS and put more resources into it.”

—Patrick Wen,
Dana-Farber Cancer Institute

models—particularly in cases where there may be residual disease. The company also is running studies to determine whether 2-HG appears in urine, cerebrospinal fluid and/or tissues besides the brain in patients with IDH1-mutant gliomas.

The authors have applied for a patent covering the method described in the *Science Translational Medicine* study.

Haas, M.-J. *SciBX* 5(5); doi:10.1038/scibx.2012.117
Published online Feb. 2, 2012

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e-mail: ovidiu@nmr.mgh.harvard.edu

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COMPANIES AND INSTITUTIONS MENTIONED

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Dana-Farber Cancer Institute, Boston, Mass.
Harvard Medical School, Boston, Mass.
Massachusetts General Hospital, Boston, Mass.
Massachusetts Institute of Technology, Cambridge, Mass.



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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
Cancer				
Bladder cancer	Keratin 14 (KRT14)	<p>Patient sample studies suggest KRT14 could help predict bladder cancer prognosis. In two sets of gene and protein expression data from bladder cancer patient samples, KRT14 expression correlated with lower overall survival. Next steps include testing whether <i>KRT14</i> can predict patient response to chemotherapy.</p> <p>SciBX 5(5); doi:10.1038/scibx.2012.118 Published online Feb. 2, 2012</p>	Patent application filed; available for licensing	<p>Volkmer, J.-P. <i>et al. Proc. Natl. Acad. Sci. USA</i>; published online Jan. 19, 2012; doi:10.1073/pnas.1120605109 Contact: Keith S. Chan, Baylor College of Medicine, Houston, Texas e-mail: kc1@bcm.edu Contact: Irving L. Weissman, Stanford University, Stanford, Calif. e-mail: irv@stanford.edu Contact: Debashis Sahoo, same affiliation as above e-mail: sahoo@stanford.edu</p>
Breast cancer	IL-20	<p>Studies in mice and in human samples suggest inhibiting IL-20 could help treat breast cancer and breast cancer-induced bone loss. In primary breast tumor samples, levels of IL-20 were inversely correlated with metastasis-free survival. In mice with mammary tumors, an anti-IL-20 antibody lowered tumor growth compared with control IgG. In mouse models of metastatic mammary cancer, the antibody decreased both the number of bone metastases and bone loss compared with control IgG. Ongoing work includes testing IL-20 inhibition in animal models of bone metastases of prostate and other cancers. NN8226 (anti-IL20), an anti-IL-20 mAb from Novo Nordisk A/S, is in Phase II testing to treat rheumatoid arthritis (RA).</p> <p>SciBX 5(5); doi:10.1038/scibx.2012.119 Published online Feb. 2, 2012</p>	Patented by National Cheng Kung University; available for licensing	<p>Hsu, Y.-H. <i>et al. J. Immunol.</i>; published online Jan. 11, 2012; doi:10.4049/jimmunol.1102843 Contact: Ming-Shi Chang, National Cheng Kung University, Tainan, Taiwan e-mail: mschang@mail.ncku.edu.tw</p>
Cancer	Lymphocyte-activation gene 3 (LAG3; CD223); PD-1 receptor (PDCD1; PD-1; CD279)	<p>Mouse studies suggest inhibiting both LAG3 and PD-1 could help treat cancer. In two mouse models of cancer, combined injection of anti-Lag3 and anti-Pd-1 antibodies increased the number of tumor-free animals compared with injection of either antibody alone. Next steps could include screening additional cancer types for responsiveness to the combination antibody therapy.</p> <p>At least six companies have antibodies or fusion proteins that target LAG3 or PD-1 in Phase II testing or earlier to treat cancer.</p> <p>SciBX 5(5); doi:10.1038/scibx.2012.120 Published online Feb. 2, 2012</p>	Patents pending; licensing status unavailable	<p>Woo, S.-R. <i>et al. Cancer Res.</i>; published online Dec. 20, 2011; doi:10.1158/0008-5472.CAN-11-1620 Contact: Dario A.A. Vignali, St. Jude Children's Research Hospital, Memphis, Tenn. e-mail: dario.vignali@stjude.org</p>

This week in therapeutics

Indication	Target/marker/pathway	Summary	Licensing status	Publication and contact information
Melanoma	Wingless-type MMTV integration site family member 3A (WNT3A); BRAF	<p>Mouse studies suggest activating WNT signaling may increase the efficacy of BRAF inhibitors in melanoma. In a xenograft mouse model of melanoma, a BRAF inhibitor plus transplantation of cells overexpressing WNT3A led to less tumor growth than a BRAF inhibitor plus transplantation of cells expressing a control protein.</p> <p>Zelboraf vemurafenib, a BRAF inhibitor from Daiichi Sankyo Co. Ltd. and Roche, is marketed to treat metastatic melanoma.</p> <p>SciBX 5(5); doi:10.1038/scibx.2012.121 Published online Feb. 2, 2012</p>	Patent applications filed; available for licensing	<p>Biechele, T.L. <i>et al. Sci. Signal.</i>; published online Jan. 10, 2012; doi:10.1126/scisignal.2002274</p> <p>Contact: Andy J. Chien, University of Washington School of Medicine, Seattle, Wash. e-mail: andchien@uw.edu</p> <p>Contact: Randall T. Moon, same affiliation as above e-mail: rtmoon@uw.edu</p>
Retinoblastoma	Spleen tyrosine kinase (SYK)	<p>Patient sample and mouse studies suggest inhibiting SYK could help treat retinoblastoma. SYK was expressed at high levels in all 82 samples from patients with retinoblastoma and was not detected in matched normal retinal tissue. In a mouse xenograft model of retinoblastoma, the small molecule SYK inhibitors BAY 61-3606 and R406 both increased survival compared with vehicle. Next steps include developing an ophthalmic formulation of R406 and measuring SYK expression in metastatic retinoblastoma. BAY 61-3606 is a research reagent. Tamatinib fosdium (R788), an oral formulation of R406 from Rigel Pharmaceuticals Inc. and AstraZeneca plc, is in Phase III testing to treat rheumatoid arthritis (RA) and in Phase II trials to treat diffuse large B cell lymphoma (DLBCL).</p> <p>At least three other companies have SYK inhibitors in clinical or preclinical testing for various indications.</p> <p>SciBX 5(5); doi:10.1038/scibx.2012.122 Published online Feb. 2, 2012</p>	Unpatented; licensing status not applicable	<p>Zhang, J. <i>et al. Nature</i>; published online Jan. 11, 2012; doi:10.1038/nature10733</p> <p>Contact: Michael A. Dyer, St. Jude Children's Research Hospital, Memphis, Tenn. e-mail: michael.dyer@stjude.org</p>
Cardiovascular disease				
Ischemia/reperfusion injury	Fibroblast growth factor 2 (FGF2); syndecan 4 (SDC4)	<p>Rat studies suggest delivering FGF2 together with SDC4-containing liposomes could help treat ischemia. In a rat model of hind limb ischemia, FGF2 plus SDC4-containing liposomes resulted in near-complete resolution of ischemia within 7 days, whereas FGF2 alone failed to resolve ischemia at day 16. In rats, FGF2 plus the liposomes increased arteriole density sevenfold and capillary density twofold compared with FGF2 alone. Next steps include optimizing a delivery system for the SDC4-containing liposomes and scaling up the manufacturing process.</p> <p>SciBX 5(5); doi:10.1038/scibx.2012.123 Published online Feb. 2, 2012</p>	Patent application filed; available for licensing from the Massachusetts Institute of Technology Technology Licensing Office	<p>Jang, E. <i>et al. Proc. Natl. Acad. Sci. USA</i>; published online Jan. 17, 2012; doi:10.1073/pnas.1117885109</p> <p>Contact: Aaron B. Baker, The University of Texas at Austin, Austin, Texas e-mail: abbaker1@gmail.com</p>

This week in therapeutics

Indication	Target/marker/ pathway	Summary	Licensing status	Publication and contact information
Genitourinary disease				
Incontinence	Muscarinic acetylcholine receptor M3 (CHRM3; HM3)	<i>In vitro</i> and rat studies suggest 1,4-dioxane-based HM3 antagonists could help treat overactive bladder (OAB). Chemical synthesis and <i>in vitro</i> testing identified two lead compounds that were selective, low nanomolar antagonists of HM3. In a rat model of OAB, the two compounds decreased volume-induced bladder contractions compared with the approved OAB drug oxybutynin without affecting mean blood pressure or heart rate. Future studies could include testing the compounds in animal models of chronic obstructive pulmonary disease (COPD), irritable bowel syndrome (IBS) and other diseases in which HM3 plays a role. Oxybutynin is a generic competitive antagonist of CHRM1 (HM1), CHRM2 (HM2) and HM3. At least seven companies market muscarinic receptor antagonists to treat OAB.	Patent and licensing status unavailable	Del Bello, F. <i>et al. J. Med. Chem.</i> ; published online Jan. 13, 2012; doi:10.1021/jm2013216 Contact: Alessandro Piergentili, University of Camerino, Camerino, Italy e-mail: alessandro.piergentili@unicam.it
Hepatic disease				
Drug-induced liver toxicity (DILI)	Gap junction protein β1, 32 kDa (GJB1; CX32; connexin-32)	Mouse studies identified a small molecule inhibitor of CX32 that could help treat DILI. Cx32 knockout mice had less liver damage than wild-type mice following challenge with the hepatotoxin thioacetamide. In mouse models of thioacetamide- and acetaminophen-induced liver toxicity, the small molecule CX32 inhibitor 2-aminoethoxydiphenyl borate (2APB) decreased liver damage and increased survival compared with vehicle control. Next steps by Heprotech Inc. include studying the potential off-target effects of inhibiting CX32 (<i>see Closing the gap on liver toxicity, page 5</i>).	Findings patented; licensed to Heprotech, which was cofounded by the corresponding author	Patel, S.J. <i>et al. Nat. Biotechnol.</i> ; published online Jan. 15, 2012; doi:10.1038/nbt.2089 Contact: Martin L. Yarmush, Massachusetts General Hospital, Boston, Mass. e-mail: ireis@sbi.org
Liver disease	IL-11 receptor	<i>In vitro</i> and mouse studies suggest agonizing the IL-11 receptor could help treat liver damage. In a mouse model of acetaminophen-induced liver injury, an IL-11 receptor agonist increased hepatocyte proliferation and decreased liver damage compared with saline control. Next steps could include increasing the activity and stability of IL-11 receptor agonists. Pfizer Inc. markets Neumega oprelvekin, an IL-11 receptor agonist, to treat thrombocytopenia. ViroMed Co. Ltd.'s VM501, an IL-11 receptor agonist, is in Phase II testing for thrombocytopenia.	Unpatented; licensing status unavailable	Nishina, T. <i>et al. Sci. Signal.</i> ; published online Jan. 17, 2012; doi:10.1126/scisignal.2002056 Contact: Hiroyasu Nakano, Juntendo University School of Medicine, Tokyo, Japan e-mail: hnakano@juntendo.ac.jp

This week in therapeutics

Indication	Target/marker/pathway	Summary	Licensing status	Publication and contact information
Infectious disease				
Pneumonia	Growth hormone-releasing hormone receptor (GHRHR)	<p>Mouse studies suggest GHRHR agonists may help treat pulmonary permeability edema, a complication of <i>Streptococcus pneumoniae</i> infection. In a mouse model of <i>S. pneumoniae</i> toxin-induced edema, the GHRHR agonist JI-34 decreased alveolar permeability and edema formation compared with no treatment. Next steps include testing the efficacy of GHRHR agonists on alveolar liquid clearance in isolated, perfused human lungs and on edema formation in <i>Pneumococcus</i>-infected mice treated with antibiotics.</p> <p>Theratechnologies Inc. markets the GHRHR agonist Egrifta tesamorelin for lipodystrophy.</p> <p>SciBX 5(5); doi:10.1038/scibx.2012.127 Published online Feb. 2, 2012</p>	Patent applications filed; available for licensing	<p>Lucas, R. <i>et al. Proc. Natl. Acad. Sci. USA</i>; published online Jan. 23, 2012; doi:10.1073/pnas.1121075109</p> <p>Contact: Andrew V. Schally, University of Miami Miller School of Medicine, Miami, Fla. e-mail: andrew.schally@va.gov</p> <p>Contact: Rudolf Lucas, Georgia Health Sciences University, Augusta, Ga. e-mail: lucas@georgiahealth.edu</p>
<i>Pseudomonas</i>	Toll-like receptor 5 (TLR5); IL-1 β	<p>Cell culture studies suggest agonizing TLR5 and IL-1β could be useful for treating pulmonary <i>Pseudomonas aeruginosa</i> infection. In cell culture, mouse alveolar macrophages lacking Tlr5 or IL-1β had lower activity against <i>P. aeruginosa</i> than wild-type macrophages. Next steps including testing whether TLR5 agonists could increase macrophage killing of <i>P. aeruginosa in vitro</i> and in animal models.</p> <p>Cleveland BioLabs Inc.'s CBLB502, a bacteria-derived TLR5 agonist, is in Phase II testing for acute radiation syndrome (ARS) and in preclinical development for colorectal cancer and renal damage.</p> <p>SciBX 5(5); doi:10.1038/scibx.2012.128 Published online Feb. 2, 2012</p>	Work unpatented; licensing status not applicable	<p>Descamps, D. <i>et al. Proc. Natl. Acad. Sci. USA</i>; published online Jan. 17, 2012; doi:10.1073/pnas.1108464109</p> <p>Contact: Jean-Michel Sallenave, Pasteur Institute, Paris, France e-mail: jms@pasteur.fr</p> <p>Contact: Bénédicte Manoury, Institut National de la Santé et de la Recherche Médicale (INSERM), Paris, France e-mail: benedicte.manoury@inserm.fr</p>
Musculoskeletal disease				
Muscular dystrophy	MicroRNA-21 (miR-21)	<p>Patient sample and mouse studies suggest inhibiting miR-21 could help treat muscular dystrophy. In muscle biopsies from patients with Duchenne muscular dystrophy (DMD), collagen and miR-21 expression was greater than that in healthy muscle. In a mouse model of DMD, injection of an antagomir against miR-21 decreased muscle fibrosis compared with injection of a control antagomir. Next steps include extended safety studies of miR-21 in the DMD mouse model.</p> <p>Regulus Therapeutics Inc.'s antagomir-21, an antisense oligonucleotide targeting miR-21, is in preclinical development for cardiac fibrosis.</p> <p>SciBX 5(5); doi:10.1038/scibx.2012.129 Published online Feb. 2, 2012</p>	Patent application filed; available for licensing from Pompeu Fabra University Contact: Pablo Garcia Mahedero, Pompeu Fabra University, Barcelona, Spain phone: +34 935 421 273 e-mail: pablo.mahedero@upf.edu	<p>Ardite, E. <i>et al. J. Cell Biol.</i>; published online Jan. 2, 2012; doi:10.1083/jcb.201105013</p> <p>Contact: Pura Muñoz-Cánoves, Pompeu Fabra University, Barcelona, Spain e-mail: pura.munoz@upf.edu</p>

This week in therapeutics

Indication	Target/marker/pathway	Summary	Licensing status	Publication and contact information
Neurology				
Amyotrophic lateral sclerosis (ALS)	AMP-activated protein kinase (AMPK)	Cell culture studies suggest inhibiting AMPK signaling could help treat SOD1-driven ALS. About 15% of familial ALS cases involve mutations in <i>superoxide dismutase 1 (SOD1)</i> . In cultured rat motor neurons, an AMPK inhibitor decreased mutant Sod1-induced cell death compared with vehicle. An AMPK activator increased mutant Sod1-induced cell death compared with vehicle. Next steps could include screening for a lead AMPK inhibitor and evaluating the compound in mammalian models of ALS. SciBX 5(5); doi:10.1038/scibx.2012.130 Published online Feb. 2, 2012	Patent and licensing status unavailable	Lim, M.A. <i>et al. J. Neurosci.</i> ; published online Jan. 18, 2012; doi:10.1523/JNEUROSCI.6554-10.2012 Contact: Robert G. Kalb, The Children's Hospital of Philadelphia, Philadelphia, Pa. e-mail: kalb@email.chop.edu
Depression	Microtubule-associated protein 2 (MAP2)	Studies in mice identified a pregnenolone derivative that could help treat depression. In a mouse model of depression, 3 β -methoxy-pregnenolone (MAP4343) decreased depression-like behavior compared with vehicle or Prozac fluoxetine. <i>In vitro</i> , MAP4343 bound MAP2 and stimulated microtubule assembly. Next steps at Mapreg S.A.S. include studying MAP343 in animal models of other neuropsychiatric disorders. Eli Lilly and Co. markets Prozac to treat major depressive disorder, obsessive-compulsive disorder (OCD), bulimia nervosa and panic disorder. SciBX 5(5); doi:10.1038/scibx.2012.131 Published online Feb. 2, 2012	Findings covered in U.S. by a pending patent; available for licensing from Mapreg	Bianchi, M. & Baulieu, E.-E. <i>et al. Proc. Natl. Acad. Sci. USA</i> ; published online Jan. 19, 2012; doi:10.1073/pnas.1121485109 Contact: Etienne-Emile Baulieu, Mapreg S.A.S., Le Kremlin-Bicetre, France e-mail: etienne.baulieu@inserm.fr
Nerve damage	Acetylcholinesterase (AChE); butyrylcholinesterase (BuChE)	Studies <i>in vitro</i> and in mice suggest amidine-oxime-based compounds could help reverse organophosphate nerve agent poisoning. Organophosphates including sarin and some pesticides covalently modify and inactivate AChE and BuChE, thus blocking neurotransmission. <i>In vitro</i> , amidine-oxime compounds increased the activity of organophosphate-inhibited AChE and BuChE compared with vehicle. In mice with organophosphate poisoning, a lead amidine-oxime compound decreased behavioral abnormalities and increased survival compared with vehicle. Next steps include IND-enabling toxicology studies. SciBX 5(5); doi:10.1038/scibx.2012.132 Published online Feb. 2, 2012	Patent pending; available for licensing	Kalisiak, J. <i>et al. J. Med. Chem.</i> ; published online Dec. 29, 2011; doi:10.1021/jm201364d Contact: John R. Cashman, Human BioMolecular Research Institute, San Diego, Calif. e-mail: jcashman@hbri.org

This week in therapeutics

Indication	Target/marker/pathway	Summary	Licensing status	Publication and contact information
Various				
Inflammation; sepsis	Rhomboid 5 homolog 2 (RHBDF2; iRhom2)	<p>Studies in cell culture and in mice suggest inhibiting iRhom2 could help treat inflammatory and autoimmune diseases. In mice or bone marrow-derived macrophages treated with lipopolysaccharide (LPS), <i>iRhom2</i> knockout decreased tumor necrosis factor (TNF) induction compared with that seen in wild-type mice or macrophages. In a mouse model of septic shock, <i>iRhom2</i> knockout mice had less TNF-α elevation and liver damage and greater survival than wild-type mice. Next steps could include screening for iRhom2 inhibitors.</p> <p>SciBX 5(5); doi:10.1038/scibx.2012.136 Published online Feb. 2, 2012</p>	Patent and licensing status for both studies unavailable	<p>Adrain, C. <i>et al. Science</i>; published online Jan. 13, 2012; doi:10.1126/science.1214400 Contact: Matthew Freeman, MRC Laboratory of Molecular Biology, Cambridge, U.K. e-mail: MF1@mrc-lmb.cam.ac.uk Contact: Markus Zettl, same affiliation as above e-mail: zettl.markus@googlemail.com</p> <p>McIlwain, D.R. <i>et al. Science</i>; published online Jan. 13, 2012; doi:10.1126/science.1214448 Contact: Tak W. Mak, University Health Network, Toronto, Ontario, Canada e-mail: tmak@uhnresearch.ca Contact: David R. McIlwain, same affiliation as above e-mail: dmcilwai@uhnresearch.ca</p>

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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			
Human induced pluripotent stem (iPS) cell-derived adipocytes to screen for obesity and diabetes therapeutics	Human iPS cell-derived adipocytes could be used to identify therapeutics for obesity and diabetes. Human iPS cell lines were differentiated into mesenchymal progenitor cells, then transduced with <i>peroxisome proliferation-activated receptor-γ</i> (<i>PPARG</i> ; <i>PPARγ</i>) either alone or in combination with <i>CCAAT enhancer binding protein-β</i> (<i>CEBPB</i> ; <i>CRP2</i>) and <i>PR domain containing 16</i> (<i>PRDM16</i>) to produce white or brown adipocytes, respectively. In mice, implantation of these adipocytes led to the formation of white or brown adipose tissue. Next steps include collaborating with Roche to identify compounds that modulate the insulin sensitivity of white adipocytes or that activate brown adipocytes (see Browning fat , page 1).	Patent applications filed; licensed nonexclusively to Roche; available for additional licensing	Ahfeldt, T. <i>et al. Nat. Cell Biol.</i> ; published online Jan. 15, 2012; doi:10.1038/ncb2411 Contact: Chad A. Cowan, Massachusetts General Hospital, Boston, Mass. e-mail: ccowan@fas.harvard.edu
SciBX 5(5); doi:10.1038/scibx.2012.137 Published online Feb. 2, 2012			
Disease models			
Mouse model of cigarette smoke-induced emphysema	A mouse model of cigarette smoke-driven emphysema could aid the development of new treatments for the disease. Mice exposed to cigarette smoke for four months had greater expression of <i>osteopontin</i> (<i>Opn</i> ; <i>Spp1</i>) than unexposed mice and developed hallmarks of emphysema that included decreased lung density and infiltration of immune cells. In the model, <i>Opn</i> knockout mice had less smoke-induced emphysema than wild-type controls. Next steps include using the model to explore the causes of smoking-related emphysema.	Unpatented; unavailable for licensing	Shan, M. <i>et al. Sci. Transl. Med.</i> ; published online Jan. 18, 2012; doi:10.1126/scitranslmed.3003041 Contact: Farrah Kheradmand, Baylor College of Medicine, Houston, Texas e-mail: farrahk@bcm.edu Contact: David B. Corry, same affiliation as above e-mail: dcorry@bcm.edu
SciBX 5(5); doi:10.1038/scibx.2012.138 Published online Feb. 2, 2012			
Drug platforms			
Depletion of tumor necrosis factor receptor superfamily member 9 (TNFRSF9; 4-1BB; CD137 ⁺ /CD4 ⁺ T cells to improve adoptive cell therapy treatment of cancer	Studies in mice and in patient samples suggest depleting CD137 ⁺ /CD4 ⁺ T cells could help increase the efficacy of adoptive cell therapy. In mice immunized with a whole-cell cancer vaccine, levels of CD137 ⁺ /CD4 ⁺ T _{reg} cells were higher than those in unimmunized mice. In a mouse model of lymphoma, transplantation of CD137 ⁻ /CD4 ⁺ T cells protected mice from lymphoma cell challenge compared with transplantation of a mixed population of CD137 ⁺ /CD4 ⁺ and CD137 ⁻ /CD4 ⁺ T cells. Next steps include testing antibody-mediated depletion of CD137 ⁺ T cells in transplantation experiments. BMS-663513, an agonistic mAb against CD137 from Bristol-Myers Squibb Co., is in Phase I/II testing to treat cancer.	Unpatented; available for licensing	Goldstein, M.J. <i>et al. Cancer Res.</i> ; published online Jan. 9, 2012; doi:10.1158/0008-5472.CAN-11-3375 Contact: Ronald Levy, Stanford University School of Medicine, Stanford, Calif. e-mail: levy@stanford.edu
SciBX 5(5); doi:10.1038/scibx.2012.139 Published online Feb. 2, 2012			

Erratum: Analysis: Cover Story

Kotz, J. *SciBX* 5(4); doi:10.1038/scibx.2012.87
Published online Jan. 26, 2012

Erratum: The Distillery: chemistry: production of N-methylated macrocyclic peptide libraries

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The Analysis item “Macrocycles by the trillions” and a Techniques item highlighting an article by Yamagishi *et al.* misstated the size of the library of N-methylated peptide macrocycles. *In vitro* translation of mRNA-linked peptides resulted in a library of about 10¹² N-methylated peptide macrocycles.

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