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By *Tim Fulmer, Senior Writer*

Researchers from **The University of Texas Southwestern Medical Center** have shown that an antibody targeting endotrophin, a fat cell-derived extracellular protein, reduced growth of breast tumors in mice.¹ The team will next study the antibody in animal models of obesity-induced cancer and test a humanized version in human cancer samples.

Over the past decade, multiple epidemiological studies have shown a strong correlation between obesity, as measured by body mass index (BMI), and incidence of various solid and hematological cancers.²⁻⁴ Moreover, animal studies have shown that adipocytes in the tumor microenvironment secrete a variety of extracellular factors, some of which influence tumor development and progression.⁵

The ongoing challenge has been to determine which of those factors are most important in driving tumor growth and figuring out how to target them.

Philipp Scherer and Jiyoun Park at the UT Southwestern Medical Center have focused their efforts on the potential role of collagen type VI (COL6) in tumorigenesis. COL6 is a multimeric glycoprotein composed of three subunits: COL6 α 1 (COL6A1), COL6A2 and COL6A3.

Scherer is professor of internal medicine and director of the Touchstone Diabetes Center and Park is assistant instructor of internal medicine at the UT Southwestern Medical Center.

Adipose tissue is the most abundant source of COL6,⁶ and research by multiple labs has shown that the target can mediate cell-cell signaling events and is upregulated in some tumor stroma.^{7,8}

In two prior mouse studies, the UT Southwestern team found that Col6 promoted tumorigenesis and Col6 knockout reduced rates of early hyperplasia and primary tumor growth.^{9,10} They also found that endotrophin—an extracellular cleavage product of the Col6a3 subunit—was highly enriched in murine and human breast cancer samples.

Based on those findings, the researchers hypothesized that endotrophin could be the portion of COL6 responsible for promoting tumor growth and that blocking the protein might have an antitumor effect. They also suspected that targeting endotrophin might be safer than targeting the entire COL6 protein, which is required for the mechanical stability of many connective tissues including blood vessels, lung, muscle and skin.

The researchers first generated transgenic mice that expressed high levels of endotrophin in the mammary gland and then crossed those animals with mice that had aggressive mammary adenocarcinoma and pulmonary metastasis.



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

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The resulting animals showed greater tumor volume and metastatic burden than mouse models with normal endotrophin expression, suggesting endotrophin enhanced both primary tumor growth and metastatic disease.

Subsequent experiments suggested a mechanism whereby endotrophin acted on both cancer cells and stromal cells to generate its effects. In cancer cells, endotrophin induced epithelial-mesenchymal transition, which led to increased metastases compared with no endotrophin. In the tumor stroma, endotrophin recruited and activated macrophages and endothelial cells, which in turn promoted tumor growth through increased angiogenesis (see Figure 1, “Targeting endotrophin in breast cancer”).

“[The paper] is a very significant advance and makes a contribution to explaining the mechanism of how adipocytes promote tumor growth.”

**—Ernst Lengyel,
The University of Chicago
Pritzker School of Medicine**

To test the effects of directly blocking endotrophin, the researchers implanted wild-type mice with primary mammary epithelial cancer cells expressing high levels of the protein and treated them with an antiendotrophin antibody.

The animals had significantly lower tumor burden than mice given a control antibody ($p < 0.05$). Histological analysis of tumor tissue showed decreased levels of stromal cell infiltration in mice receiving the antibody, confirming that endotrophin acted at least partly through stromal cells to trigger its tumorigenic effects.

The findings were published in *The Journal of Clinical Investigation*.

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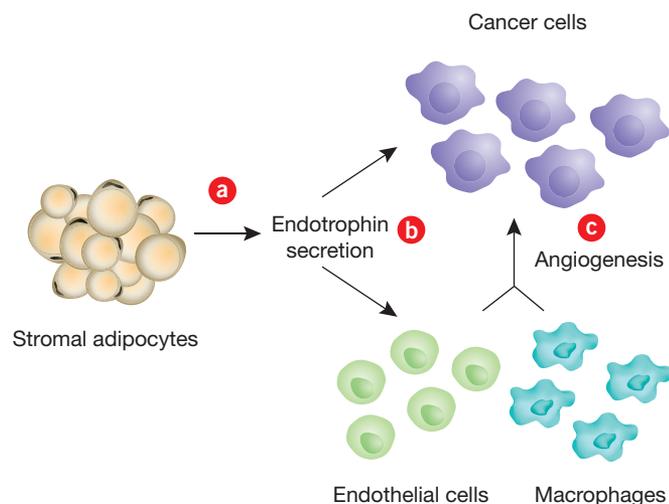


Figure 1. Targeting endotrophin in breast cancer. Researchers from **The University of Texas Southwestern Medical Center** published in *The Journal of Clinical Investigation* that blocking the extracellular protein endotrophin reduced breast tumor growth and metastasis.

Adipocytes in the tumor stroma secrete multiple factors that interact with other stromal cell types as well as tumor cells [a]. The *JCI* paper identified endotrophin, an extracellular cleavage product of collagen VI (COL6), as a factor that influenced both cancer cells and stromal cells [b]. In cancer cells, endotrophin induced the epithelial-mesenchymal transition, which led to increased metastases. In the tumor stroma, endotrophin recruited and activated macrophages and endothelial cells, which in turn promoted tumor growth through increased angiogenesis [c].

The paper “is a very significant advance and makes a contribution to explaining the mechanism of how adipocytes promote tumor growth,” said Ernst Lengyel, professor of gynecologic oncology at **The University of Chicago Pritzker School of Medicine**.

In 2011, Lengyel and colleagues published in *Nature Medicine* that ovarian cancer cells used adipocyte-derived lipids for tumor growth *in vitro* and in mice.¹¹

“Both the new *JCI* paper and our study show that adipocytes are not quiet, fat-containing cells but a very active and underappreciated component of the microenvironment which promotes tumor growth,” said Lengyel.

Fattening up

Blocking endotrophin secreted by adipose tissue could be combined with approaches that target other adipocyte-derived factors to prevent tumorigenesis, said Jian-Wei Gu, assistant professor of physiology and biophysics at **The University of Mississippi Medical Center**.

In 2011, Gu and colleagues published data in *Cancer Biology & Therapy* showing that postmenopausal obesity in mice increased breast tumor weight compared with that in nonobese controls. The obese mice also had substantially higher levels of Vegf in the serum and visceral fat, suggesting adipose tissue expressed high levels of VEGF, which promoted tumor growth.¹²

Based on those findings, Gu said he is now testing anti-VEGF therapies in mouse models of postmenopausal obesity-associated breast cancer.

Corresponding author Scherer told *SciBX* his team will next study the antiendotrophin mAb in additional mouse models of obesity-associated malignancies, initially focusing on breast and colon cancers. “We also plan to humanize the antibody and test it in human breast and colon cancer samples,” he said.

The *JCI* findings are not patented, Scherer said.

Fulmer, T. *SciBX* 5(41); doi:10.1038/scibx.2012.1071
Published online Oct. 18, 2012

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COMPANIES AND INSTITUTIONS MENTIONED

The University of Chicago Pritzker School of Medicine,
Chicago, Ill.

The University of Mississippi Medical Center, Jackson, Miss.

The University of Texas Southwestern Medical Center,
Dallas, Texas

EZH2 moves

By Joanne Kotz, Senior Editor

Epizyme Inc. and GlaxoSmithKline plc have independently reported small molecule inhibitors of histone methyltransferase enhancer of zeste homolog 2 that showed efficacy in preclinical models of lymphomas with activating mutations of the target.^{1,2} Both companies plan to take inhibitors of the histone methyltransferase into the clinic in cancer.

Epizyme initially will focus on non-Hodgkin's lymphoma (NHL) patients with activating mutations in *enhancer of zeste homolog 2* (*EZH2*). GSK declined to disclose how it will select a specific patient population. Neither company disclosed timing for an IND.

EZH2 is the catalytic subunit of polycomb repressive complex 2 (PRC2) and represses gene transcription by adding methyl groups to histone H3 lysine 27 (H3K27). Amplification or overexpression of *EZH2* and other components of PRC2 occurs in a variety of cancers, including breast cancer and lymphoma.

Even more compelling are results showing that *EZH2* mutational status might help select patients who would respond to *EZH2* inhibition.

In 2010, researchers at Epizyme first reported that somatic point mutations in Tyr641 lead to a gain in *EZH2*-catalyzed trimethylation of H3K27 (H3K27me3).³ Mutations at this site and other sites that were subsequently shown to increase *EZH2* activity occur in about 10%–20% of NHL cases.

Now, Epizyme and GSK have taken steps toward pharmacologically validating *EZH2* as a target in this subset.

Both companies conducted high throughput screens to look for PRC2 inhibitors. Optimization of the lead hits resulted in the identification of EPZ005687 by Epizyme and GSK126 by the GSK team. The compounds inhibited enzyme activity with K_i values of about 25 nM and 1 nM, respectively.

Importantly, both molecules inhibited mutant and wild-type *EZH2* with similar potency, which meant the researchers could study the effects of blocking *EZH2* in cancers with mutant and wild-type versions of the target.

The teams looked at the effects of inhibiting *EZH2* in lymphoma cell lines with mutant and wild-type *EZH2* and found mutational status is a major—but not sole—determinant of lymphoma cell sensitivity to *EZH2* inhibition.

EPZ005687 decreased cell proliferation in two NHL cell lines with activating mutations but not in a cell line containing wild-type *EZH2*.

GSK126 decreased cell proliferation in six of nine cell lines tested that contained mutant *EZH2*. On the other hand, 35 of 37 lymphoma cell lines containing wild-type *EZH2* were resistant to *EZH2* inhibition.

Epizyme published its results in *Nature Chemical Biology*. The GSK team reported its findings in *Nature*.

“Clearly, the most important finding is the discovery of potent and selective small molecule *EZH2* inhibitors. This represents an important step in the maturation of *EZH2* as a drug discovery target,” said Patrick Trojer, senior director and head of biology at epigenetics company **Constellation Pharmaceuticals Inc.**

Constellation has a preclinical program targeting *EZH2*. Trojer said the company has identified selective small molecule inhibitors

of *EZH2* and is optimizing and testing them in preclinical cancer models.

“These two landmark papers define a novel chemotype that selectively inhibits mutant and wild-type *EZH2* and provide pharmacologic target validation of the enzymatic function of somatically altered *EZH2* in non-Hodgkin's lymphoma,” added James Bradner.

Bradner is an investigator in the Department of Medical Oncology at **Dana-Farber Cancer Institute** and assistant professor in the Department of Medicine at **Harvard Medical School**. He also is a founder of epigenetics companies **Acetylon Pharmaceuticals Inc.** and **Tensha Therapeutics Inc.**

A path to the clinic

Epizyme and partner **Eisai Co. Ltd.** have identified the molecule they expect to take into the clinic and hope to submit an IND “in the very near future,” according to Epizyme EVP and CSO Robert Copeland. Epizyme's lead molecule comes from a distinct chemical series from EPZ005687 and “as an initial indication we'll be targeting *EZH2* mutant-bearing non-Hodgkin's lymphomas,” he noted.

GSK continues to have an active *EZH2* inhibitor program, said Caretha Creasy, director of biology and translational medicine at GSK. She did not specify GSK's patient selection strategy or the company's timing for entering the clinic, but she did say that in NHL, “*EZH2* mutation plus high levels of H3K27me3 predicted sensitivity very well, which would be an obvious selection criterion for the clinic.”

Both companies also are exploring other cancer subtypes in which *EZH2* inhibitors might work, although GSK is not disclosing which cancers.

Epizyme is looking at cancers in which PRC2 subunits are known to be amplified, including prostate, breast and esophageal cancers and myeloma, said Copeland.

Looking for markers

There are other oncogenic alterations besides mutant *EZH2* that could result in tumor sensitivity to *EZH2* inhibition, and these genetic alterations could be used to define patient populations.

One potential marker for *EZH2* efficacy is genetic alternations of lysine-specific demethylase 6A (KDM6A; *UTX*), a histone demethylase that removes methyl groups from H3K27. Inactivation of *UTX* leads to higher levels of H3K27me3, similarly to activating mutations in *EZH2*.

“An exploration of these *EZH2* inhibitors more broadly in cancer, specifically in *UTX* mutated or deleted tumor models, is an obvious and important next step for this research,” said Bradner.

In addition to *UTX* mutations as a potential marker, Trojer noted that “prostate cancers frequently carry a heterozygous deletion of miR-101, a microRNA that attenuates *EZH2* expression. Thus, prostate cancer cases with miR-101 deletions have elevated levels of *EZH2* and might be dependent on *EZH2* activity.”

“An exploration of these *EZH2* inhibitors more broadly in cancer, specifically in *UTX* mutated or deleted tumor models, is an obvious and important next step for this research.”

—James Bradner
Dana-Farber Cancer Institute

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Black mamba takes away pain

By Lev Osherovich, Senior Writer

A French team has identified a pair of peptides, mambalgin-1 and mambalgin-2, from black mamba venom that could be useful for treating pain.¹ The peptides, which inhibit a class of acid-sensing ion channels on the surface of neurons, are licensed to **Theralpha S.A.S.**

Team leader Eric Lingueglia, a research director at the **Institut National de la Santé et de la Recherche Médicale** (INSERM), the Institute of Molecular and Cellular Pharmacology at **Centre National de la Recherche Scientifique** (CNRS) and the **University of Nice Sophia Antipolis**, said the analgesic peptides are nontoxic and are likely used by the snake to anesthetize its prey while other, toxic molecules do the killing.

“Venoms have been known for a long time as a source of interesting molecules, mostly toxins,” he said. “These often work by blocking ion channels, which are important for neuronal excitability and other neural functions. It was also known that venoms contain other molecules such as analgesics. Mambalgins represent less than 0.5% of the total venom.”

Lingueglia’s team uncovered the analgesic effects of mambalgins while hunting for antagonists of acid-sensing ion channels, a family of membrane-bound proteins previously implicated in multiple neurological functions including pain and anxiety.²

In frog eggs transfected with rat homologs of acid-sensing ion channel-1 (*Asic1*) and *Asic2*, black mamba venom prevented activation of the channels.

The team purified the mambalgin peptides from the venom and showed that they inhibited *Asic1* and *Asic2* activation in several cultured mammalian cell types. The two peptides differed by only a single amino acid and behaved similarly in cell culture assays.

(Continued from “EZH2 moves,” p. 4)

Epizyme has patents and patent applications covering composition of matter, methods of screening and methods of clinical use around EZH2. The program is partnered with Eisai. GSK declined to disclose the patent and licensing status of its work.

Kotz, J. *SciBX* 5(41); doi:10.1038/scibx.2012.1072
Published online Oct. 18, 2012

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Because of the near-identical behavior of the peptides, the team chose one—mambalgin-1—for further study. In mice, intrathecal injections of the peptide decreased sensitivity to inflammatory pain as potently as injections of morphine.

Lingueglia suspects ASIC1 and ASIC2 may form a heterodimeric complex that is particularly sensitive to mambalgins. Previously, the two channels were thought to act as independent homodimers.

The team found that the analgesic effect of mambalgin could be mimicked by intrathecal injection of small interfering RNA that knocked down expression of *Asic2* in the CNS.

Results were published in *Nature*.

Snake juice

One big question is what signaling pathway downstream of ASIC1 and ASIC2 mediates the analgesic effect of mambalgins. Because treatment with the opioid-signaling antagonist naloxone did not fully block the analgesic effects of mambalgin injection, Lingueglia suspects the snake venom peptides work by a mechanism distinct from that for opiates.

His team is now working out the downstream effects of mambalgin signaling in a variety of mouse pain models.

Lingueglia thinks mambalgins could be a good starting point for new pain therapeutics. He noted that modeling studies of the peptides’ structure suggest they are

compact and stable molecules that would be well-suited for use as injectable therapeutics.

“The peptide from the venom has evolved to be a very robust peptide and very stable, so it could be a drug candidate, but it’s possible that there are other molecules that could block the same target,” said Lingueglia.

Lingueglia and the University of Nice Sophia Antipolis have received a patent covering the use of mambalgins for pain.

The university has licensed the patent to Theralpha, which has a formulation of mambalgin, called THA904, in preclinical

(Continues on p. 6)

“The peptide from the venom has evolved to be a very robust peptide and very stable, so it could be a drug candidate, but it’s possible that there are other molecules that could block the same target.”

—Eric Lingueglia,
University of Nice Sophia Antipolis

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COMPANIES AND INSTITUTIONS MENTIONED

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Constellation Pharmaceuticals Inc., Cambridge, Mass.
Dana-Farber Cancer Institute, Boston, Mass.
Eisai Co. Ltd. (Tokyo:4523; Osaka:4523), Tokyo, Japan
Epizyme Inc., Cambridge, Mass.
GlaxoSmithKline plc (LSE:GSK; NYSE:GSK), London, U.K.
Harvard Medical School, Boston, Mass.
Tensha Therapeutics Inc., Cambridge, Mass.

pharmacokinetic and toxicology studies. The company could not be reached for comment.

Theralpha previously licensed three other analgesic compounds from the university. The study's coauthor, Michel Lazdunski, is CSO and SVP at Theralpha and a professor at the CNRS Institute of Molecular and Cellular Pharmacology at the University of Nice Sophia Antipolis.

Osherovich, L. *SciBX* 5(41); doi:10.1038/scibx.2012.1073
Published online Oct. 18, 2012

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Self-contained tissue factories

By Tracey Baas, Senior Editor

Cell therapy for liver disease typically involves delivery of hepatocytes to the liver intraportal vein, which carries a risk of hemorrhage, elevated portal pressure and portal vein thrombosis. Now, a **University of Pittsburgh School of Medicine** team thinks it has found a better delivery route—the lymph nodes. The team has mouse data demonstrating that transplantation of cells into lymph nodes led to generation of ectopic tissue that exhibited liver function,¹ and the group is testing the approach in pig models of liver failure.

The Pittsburgh team previously showed that intraperitoneal injection of hepatocytes rescued mice from liver failure if the transplanted cells migrated to and colonized nearby lymph nodes.² The result made sense, as the lymph nodes are highly vascularized, provide direct access to essential nutrients and growth factors found in the blood, and contain cells that secrete chemokines that enhance cell recruitment and can sustain growth of diverse tissue types.

For the new study, the team opted to directly inject hepatocytes into jejunal lymph nodes located within the peritoneal cavity. In a mouse model of lethal metabolic liver failure, transplantation of syngeneic hepatocytes led to engraftment in the nodes, persistence for more than 25 weeks and rescue of the animals from liver failure. The findings were reproduced using popliteal, axillary and periportal lymph nodes, showing that multiple nodes can support engraftment and organ rescue.

In mice, the researchers generated the equivalent of about 70% of normal liver mass in one lymph node. About 30% of normal liver mass provides minimum hepatic function in a human.³

Mice also were rescued from liver failure with allogeneic hepatocyte transfer in combination with immunosuppressive agents to prevent rejection.

The researchers also saw positive results in models of pancreatic and thymic function.

In a mouse model of diabetes, islets transplanted into the lymph nodes engrafted, produced C-peptide and glucagon and restored blood glucose levels to those of normal mice within six weeks. One mouse showed normal blood glucose levels at six months post-transplant.

In athymic nude mice, transplantation of minced thymus tissue to lymph nodes led to engraftment and the presence of T cells in the peripheral blood for at least 10 months. Those T cells mounted proper responses against tumor cell transplants.

Together, the findings provide the first example that lymph nodes may be a useful ectopic site for functional cellular transplant to restore organ function.

Results were published in *Nature Biotechnology*.

“The lymph node is an intriguing location for cell therapy, since metastatic cancer cells grow here and now we find injected healthy liver cells can also grow in lymph nodes,” said Sanjeev Gupta, professor of gastroenterology and liver diseases and chair of translational medicine at the **Albert Einstein College of Medicine of Yeshiva University**. “While the mouse studies do show some aspect of liver function in transplanted

cells and rescue of diseased animals, we need answers to more questions about the level of liver functions that may be supported in lymph nodes. For instance, would transplanted cells in lymph nodes reproduce all types of functions present in the liver, and if so, will those functions be at adequate levels and persist indefinitely?”

“I look forward to further characterization of tissue functions, especially in additional models of liver failure, including drug-induced acute liver toxicity with impaired liver regeneration. But the current findings are exciting and provide the basis for developing this new concept,” added Gupta.

Johannes Zakrzewski noted that “the technique may be useful in situations when the liver is failing slowly, and animal models should be picked appropriately.” Zakrzewski is a pediatric oncologist and a researcher who specializes in cell therapy and bone marrow transplantation at **Memorial Sloan-Kettering Cancer Center**.

“Important next steps for the team should be a GMP-grade system for obtaining the cells and using larger, more clinically relevant animal models, such as swine or primate, for scaled-up transplantation and long-term follow up to characterize engraftment and function of the transplants,” continued Zakrzewski. “Mice are not the best for long-term studies because they have life spans of about two years. Because liver transplants are often performed on individuals 50 years or older, it might also be interesting to attempt transplantation in aged large animals.”

Tim Bertram, president of R&D and CSO at **Tengion Inc.**, had a balanced view about the new method. “On the one hand, the lymph node does provide a potentially more practical, minimally invasive site for cell delivery” than intraportal vein injection, he said. “It also provides an ideal location to produce biological molecules that can be transported by the lymph circulation system to other areas of the body where they would be active by escaping immediate liver metabolism. On the other hand, the results are less exciting to me if they can’t induce an immunological benefit, such as tolerance from the lymph node injection, and still need to use immunosuppression.”

Tengion’s Neo-Urinary Conduit is in Phase I testing. The product is made from a combination of a patient’s own cells and other materials to allow urine flow from the kidneys to outside the body after radical cystectomy in patients with bladder cancer.

Zakrzewski said irradiation of the patient’s thymus could potentially avoid the need for immunosuppressants. Once the patient’s thymus is weakened, thymus tissue from the hepatocyte donor could first be transplanted to one set of lymph nodes to provide an immune system tolerant to the donor hepatocytes. The hepatocytes could then be transplanted to another set of lymph nodes to provide liver function.

“While the mouse studies do show some aspect of liver function in transplanted cells and rescue of diseased animals, we need answers to more questions about the level of liver functions that may be supported in lymph nodes.”

— Sanjeev Gupta,
Albert Einstein College of
Medicine of Yeshiva University

Going to the pigs

“Our first ongoing studies are focusing on transplanting hepatocytes to the lymph nodes in pig models of surgically induced liver injury,”

said Eric Lagasse, leader of the Pittsburgh group. “We want to see if we can rescue organ function in larger animals that will require greater numbers of transplanted cells than those used in mice. We showed that mice could be rescued by modifying one lymph node. For pigs, we will be determining how many lymph nodes will have to be modified to generate enough ectopic organ mass for rescue.”

“Yes, we could work with older pigs, but there is no evidence that liver regeneration fails in older recipients,” Lagasse continued. “I don’t foresee regeneration issues in patients older than 50; patients older than 80 might be more relevant.”

Lagasse is associate professor of pathology and director of the Cancer Stem Cell Center at the **McGowan Institute for Regenerative Medicine** at the University of Pittsburgh School of Medicine.

The human body contains about 500–600 lymph nodes, so “we don’t foresee manipulating multiple nodes to present a problem,” he said. “Cancer patients that have had lymph nodes removed during surgery for their cancer have functional immune systems.”

He added, “We’re going to be realistic by first focusing on allogeneic transplant using hepatocytes obtained from organs, which will require immunosuppression. But the far-reaching hope is that in the future hepatocytes will be obtained from induced pluripotent stem cells derived from patient fibroblasts, thus circumventing the need for suppression.”

“For now, we have experiments in progress to investigate the concept mentioned [by Zakrzewski],” Lagasse told *SciBX*. “We are working to demonstrate that induced tolerance is possible by transplanting thymus plus cells or transplanting thymus plus an organ from the same donor. This should provide a way to circumvent the need for immunosuppressants in the near future.”

University of Pittsburgh School of Medicine has filed for a patent covering the findings. The IP is available for licensing.

Baas, T. *SciBX* **5(41)**; doi:10.1038/scibx.2012.1074

Published online Oct. 18, 2012

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Contact: Eric Lagasse, University of Pittsburgh School of Medicine, Pittsburgh, Pa.
e-mail: lagasse@pitt.edu
2. Hoppo, T. *et al.* *Gastroenterology* **140**, 656–666 (2011)
3. Lo, C.-M. *et al.* *Transplantation* **68**, 1112–1116 (1999)

COMPANIES AND INSTITUTIONS MENTIONED

Albert Einstein College of Medicine of Yeshiva University, New York, N.Y.

McGowan Institute for Regenerative Medicine, Pittsburgh, Pa.

Memorial Sloan-Kettering Cancer Center, New York, N.Y.

Tengion Inc. (OTCQB:TNGN), Winston-Salem, N.C.

University of Pittsburgh School of Medicine, Pittsburgh, Pa.

This week in therapeutics

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

This week in therapeutics includes important research findings on targets and compounds, grouped first by disease class and then alphabetically by indication.

Indication	Target/marker/pathway	Summary	Licensing status	Publication and contact information
Autoimmune disease				
Inflammatory bowel disease (IBD)	Cannabinoid CB ₂ receptor (CNR2)	<i>In vitro</i> and mouse studies identified selective CNR2 agonists that could help treat IBD. Radioligand displacement assays identified 4-oxo-1,4-dihydropyridines that were potent and selective inhibitors of human CNR2 over CNR1. In a mouse model of chemical-induced colitis, intraperitoneal treatment with the agonists decreased bowel thickening and ulceration compared with vehicle treatment and had an effect comparable to that of the positive control Pentasa mesalamine. Next steps could include optimizing the compounds for metabolic stability. At least six companies have CNR2 agonists in clinical and preclinical development to treat various conditions. Shire plc markets Pentasa to treat IBD.	Patent and licensing status unavailable	El Bakali, J. <i>et al. J. Med. Chem.</i> ; published online Sept. 28, 2012; doi:10.1021/jm3008568 Contact: Régis Millet, University of Lille North of France, Lille, France e-mail: regis.millet@univ-lille2.fr
SciBX 5(41); doi:10.1038/scibx.2012.1075 Published online Oct. 18, 2012				
Multiple sclerosis (MS)	Prostacyclin receptor (PTGIR)	Mouse studies suggest PTGIR agonists could help treat MS. In cocultures of mouse cortical neurons and vascular endothelial cells, prostacyclin secreted by endothelial cells or the prostacyclin analog iloprost promoted axonal sprouting and neurite growth. In mouse models of experimental autoimmune encephalomyelitis (EAE), intrathecal delivery of iloprost increased neuronal remodeling around the lesion site compared with vehicle and promoted hind limb motor recovery. Planned studies include determining whether prostacyclin or PTGIR agonists could treat relapsing-remitting MS. Bayer AG and Actelion Ltd. market Ventavis iloprost, an inhaled prostacyclin analog, to treat hypertension and have the compound in Phase II testing to treat acute lung injury.	Patent and licensing status undisclosed	Muramatsu, R. <i>et al. Nat. Med.</i> ; published online Oct. 7, 2012; doi:10.1038/nm.2943 Contact: Toshihide Yamashita, Osaka University, Osaka, Japan e-mail: yamashita@molneu.med.osaka-u.ac.jp
SciBX 5(41); doi:10.1038/scibx.2012.1076 Published online Oct. 18, 2012				
Cancer				
Breast cancer	Endotrophin	Mouse studies suggest antagonizing endotrophin could help treat breast cancer. Endotrophin is a cleaved protein derived from collagen type VI $\alpha 3$ (COL6A3). In a mouse model of aggressive mammary adenocarcinoma, endotrophin overexpression in the mammary gland led to increased tumor volume and lung metastases compared with no overexpression. In mice implanted with endotrophin-overexpressing mammary tumors, an antiendotrophin mAb significantly decreased tumor burden compared with IgG control. Next steps include humanizing the antiendotrophin mAb and testing it on human breast and colon cancer samples (<i>see Taking the fat out of cancer, page 1</i>).	Unpatented; licensing status not applicable	Park, J. & Scherer, P.E. <i>J. Clin. Invest.</i> ; published online Oct. 8, 2012; doi:10.1172/JCI63930 Contact: Philipp E. Scherer, The University of Texas Southwestern Medical Center, Dallas, Texas e-mail: philipp.scherer@utsouthwestern.edu
SciBX 5(41); doi:10.1038/scibx.2012.1077 Published online Oct. 18, 2012				

This week in therapeutics

Indication	Target/marker/pathway	Summary	Licensing status	Publication and contact information
Breast cancer	Not applicable	<p>Computational analysis of breast cancer samples from patients suggests therapeutic strategies used to treat ovarian cancer could help treat a class of basal-like breast tumors. Computational analysis of genomic and proteomic data from primary breast cancer samples identified basal-like breast tumors as a class with features similar to those of serous ovarian cancer. The data suggest patients with this class of breast tumors might benefit from treatment with poly(ADP-ribose)polymerase (PARP) inhibitors and/or platinum compounds used to treat serous ovarian cancer. Next steps could include clinical trials.</p> <p>Abbott Laboratories has the PARP inhibitor veliparib in Phase I and Phase II trials to treat multiple types of cancer. AstraZeneca plc has the PARP inhibitor Olaparib in Phase I testing to treat brain cancer and Phase II trials to treat solid tumors.</p> <p>BioMarin Pharmaceutical Inc. has BMN-673 in Phase I/II trials to treat hematologic malignancies and solid tumors.</p> <p>SciBX 5(41); doi:10.1038/scibx.2012.1078 Published online Oct. 18, 2012</p>	Unpatented; licensing status not applicable	<p>The Cancer Genome Atlas Network. <i>Nature</i>; published online Sept. 23, 2012; doi:10.1038/nature11412</p> <p>Contact: Charles M. Perou, The University of North Carolina at Chapel Hill, Chapel Hill, N.C. e-mail: cperou@med.unc.edu</p>
Liver cancer	Notch 1 (NOTCH1)	<p>Mouse studies suggest suppressing NOTCH1 signaling could help treat intrahepatic cholangiocarcinomas (ICCs). In mice with labeled hepatocytes and chondrocytes, chemically induced ICC was traced to biliary lineage cells that were derived from hepatocytes rather than from chondrocytes. In mice, expression of a constitutively active Notch1 fragment in hepatocytes increased hepatocyte conversion to biliary lineage cells and malignant progression of ICC compared with no expression of the Notch1 fragment. In a separate study, overexpression of the NOTCH1 receptor intracellular domain in the livers of wild-type mice and delivery of a protein kinase B (PKB; PKBA; AKT; AKT1)-expressing vector resulted in tumors with ICC features. Fluorescence labeling showed that hepatocytes formed biliary lineage cells and ultimately differentiated into the tumors. Next steps include determining whether NOTCH inhibitors could suppress conversion of hepatocytes to biliary lineage cells.</p> <p>Aileron Therapeutics Inc. has a stapled peptide NOTCH1 inhibitor in preclinical testing to treat acute lymphoblastic leukemia (ALL).</p> <p>Aveo Pharmaceuticals Inc.'s AV-232, a mAb targeting NOTCH1, is in preclinical testing to treat cancer.</p> <p>OncoMed Pharmaceuticals Inc.'s OMP-52M51, an anti-NOTCH1 antibody, is in preclinical testing to treat solid tumors.</p> <p>SciBX 5(41); doi:10.1038/scibx.2012.1079 Published online Oct. 18, 2012</p>	<p>Findings in first study unpatented; unavailable for licensing</p> <p>Patent and licensing status unavailable for findings in second study</p>	<p>Sekiya, S. & Suzuki, A. <i>J. Clin. Invest.</i>; published online Oct. 1, 2012; doi:10.1172/JCI63065</p> <p>Contact: Atsushi Suzuki, Kyushu University, Fukuoka, Japan e-mail: suzukicks@bioreg.kyushu-u.ac.jp</p> <p>Fan, B. <i>et al. J. Clin. Invest.</i>; published online July 17, 2012; doi:10.1172/JCI63212</p> <p>Contact: Holger Willenbring, University of California, San Francisco, Calif. e-mail: willenbring@stemcell.ucsf.edu</p>

This week in therapeutics

Indication	Target/marker/pathway	Summary	Licensing status	Publication and contact information
Non-Hodgkin's lymphoma (NHL)	Enhancer of zeste homolog 2 (EZH2)	<p>Mouse and <i>in vitro</i> studies suggest inhibiting EZH2 could help treat NHL characterized by <i>EZH2</i>-activating mutations. <i>In vitro</i>, EPZ005687 from Epizyme Inc. and GSK126 from GlaxoSmithKline plc inhibited wild-type and mutant <i>EZH2</i> with low nanomolar K_i values. In most NHL cell lines bearing <i>EZH2</i>-activating mutations, EPZ005687 and/or GSK126 decreased cell proliferation compared with vehicle. In a mouse xenograft model of <i>EZH2</i> mutant NHL, GSK126 led to tumor regression and increased survival compared with vehicle. Next steps include additional preclinical studies to prepare for Phase I clinical trials.</p> <p>GlaxoSmithKline has a preclinical program targeting EZH2 in cancer.</p> <p>Epizyme and partner Eisai Co. Ltd. have a preclinical program targeting EZH2 in NHL and breast cancer.</p> <p>Constellation Pharmaceuticals Inc. has a preclinical program targeting EZH2 in cancer (<i>see EZH2 moves, page 4</i>).</p> <p>SciBX 5(41); doi:10.1038/scibx.2012.1080 Published online Oct. 18, 2012</p>	<p>Findings in first study covered by patents and patent applications; partnered with Eisai</p> <p>Patent and licensing status undisclosed for findings in second study</p>	<p>Knutson, S.K. <i>et al. Nat. Chem. Biol.</i>; published online Sept. 30, 2012; doi:10.1038/nchembio.1084 Contact: Kevin W. Kuntz, Epizyme Inc., Cambridge, Mass. e-mail: kkuntz@epizyme.com</p> <p>McCabe, M.T. <i>et al. Nature</i>; published online Oct. 10, 2012; doi:10.1038/nature11606 Contact: Caretha L. Creasy, GlaxoSmithKline plc, Collegeville, Pa. e-mail: caretha.l.creasy@gsk.com</p>
Pancreatic cancer	Toll-like receptor 7 (TLR7)	<p>Patient sample and mouse studies suggest inhibiting TLR7 could help treat pancreatic cancer. In patient samples, TLR7 expression was greater in invasive pancreatic cancer than in preinvasive pancreatic intraepithelial neoplasias. In a mouse model of pancreatic cancer, oligonucleotide-mediated inhibition of TLR7 prevented malignant progression and stromal expansion. Next steps could include evaluating TLR7 inhibitors in animal models of pancreatic cancer.</p> <p>At least four companies have compounds that inhibit TLR7 in Phase I testing or earlier to treat autoimmune- and inflammation-related conditions.</p> <p>SciBX 5(41); doi:10.1038/scibx.2012.1081 Published online Oct. 18, 2012</p>	<p>Patent and licensing status unavailable</p>	<p>Ochi, A. <i>et al. J. Clin. Invest.</i>; published online Oct. 1, 2012; doi:10.1172/JCI63606 Contact: George Miller, New York University School of Medicine, New York, N.Y. e-mail: george.miller@med.nyu.edu</p>
Small cell lung cancer	B cell lymphoma 2 (BCL-2; BCL2); Bcl-X _L	<p>Cell culture and mouse studies identified inhibitors of BCL-2 and Bcl-X_L that could help treat small cell lung cancer. In human small cell lung cancer lines, 4,5-diphenyl-1H-pyrrole-3-carboxylic acid-based BCL-2 and Bcl-X_L inhibitors designed using structure-based optimization induced cell death more potently than clinical-stage inhibitors, including ABT-263. In mouse xenograft models of human small cell lung cancer, the most potent inhibitor induced apoptosis and tumor regression that prevented tumor growth for at least 15 days. Next steps could include testing the inhibitors in additional animal models of small cell lung cancer.</p> <p>Abbott Laboratories and Roche's Genentech Inc. unit have the BCL-2-family protein inhibitor ABT-263 in Phase I/II testing to treat small cell lung cancer.</p> <p>At least seven other companies have inhibitors of BCL-2-family proteins in clinical and preclinical testing to treat cancers.</p> <p>SciBX 5(41); doi:10.1038/scibx.2012.1082 Published online Oct. 18, 2012</p>	<p>Patent and licensing status unavailable</p>	<p>Chen, J. <i>et al. J. Med. Chem.</i>; published online Oct. 2, 2012; doi:10.1021/jm3010306 Contact: Shaomeng Wang, University of Michigan, Ann Arbor, Mich. e-mail: shaomeng@umich.edu</p>

This week in therapeutics

Indication	Target/marker/ pathway	Summary	Licensing status	Publication and contact information
Cardiovascular disease				
Arrhythmia	Potassium channel Kv11.1 (KCNH2; hERG)	High throughput screening and rabbit studies identified a modulator of ERG activity that could help prevent drug-induced arrhythmias. In rabbits, pretreatment with the lead hit decreased the incidence of Tikosyn dofetilide-induced arrhythmias compared with no treatment. Next steps could include evaluating the compound in combination with other arrhythmogenic drugs. Tikosyn, a selective potassium channel blocker from Pfizer Inc. is marketed to maintain normal sinus rhythm in patients with atrial fibrillation and/or atrial flutter arrhythmias.	Patent and licensing status unavailable	Potet, F. <i>et al. J. Biol. Chem.</i> ; published online Oct. 2, 2012; doi:10.1074/jbc.M112.380162 Contact: Sabina Kupersmidt, Vanderbilt University School of Medicine, Nashville, Tenn. e-mail: sabina.kupersmidt@vanderbilt.edu
SciBX 5(41); doi:10.1038/scibx.2012.1083 Published online Oct. 18, 2012				
Myocardial infarction (MI)	MicroRNA-34a (miR-34a); miR-34b; miR-34c	Mouse studies suggest locked nucleic acids (LNAs) that inhibit the miR-34 family could promote recovery following MI. In mouse models of MI and cardiac stress, subcutaneous injection of an anti-miR-34 LNA that silenced miR-34a, miR-34b and miR-34c led to less pathological left ventricular cardiac remodeling and cardiac hypertrophy than injection of nontargeting control LNAs. In the models, the anti-miR-34 LNA also increased cardiac function and decreased lung congestion. Next steps include evaluating the anti-miR-34 LNAs in large animal models.	Patent and licensing status undisclosed	Bernardo, B.C. <i>et al. Proc. Natl. Acad. Sci. USA</i> ; published online Oct. 9, 2012; doi:10.1073/pnas.1206432109 Contact: Julie R. McMullen, Baker IDI Heart & Diabetes Institute, Melbourne, Victoria, Australia e-mail: julie.mcmullen@bakeridi.edu.au
SciBX 5(41); doi:10.1038/scibx.2012.1084 Published online Oct. 18, 2012				
Endocrine/metabolic disease				
Diabetes	VEGF-B	Mouse studies suggest antagonizing VEGF-B could be useful for treating type 2 diabetes. In mouse models of the disease, <i>Vegf-b</i> knockouts or mice treated with an anti-Vegf-b mAb had lower lipid accumulation in peripheral tissues and greater glucose uptake than wild-type mice or mice given a control mAb. Next steps include completing preclinical toxicology studies with a humanized anti-VEGF-B mAb. CSL Ltd. has the humanized mAb in preclinical development for cardiovascular and metabolic indications.	Covered by issued and pending patents from CSL and the Ludwig Institute for Cancer Research Ltd.; available for partnering	Hagberg, C.E. <i>et al. Nature</i> ; published online Sept. 26, 2012; doi:10.1038/nature11464 Contact: Ulf Eriksson, Karolinska Institute, Stockholm, Sweden e-mail: ulf.pe.eriksson@ki.se
SciBX 5(41); doi:10.1038/scibx.2012.1085 Published online Oct. 18, 2012				
Diabetic cardiomyopathy	Ceramide synthase 5 (CERS5; LASS5)	Studies in cell culture and in mice suggest antagonizing CERS5 could be useful for treating diabetic cardiomyopathy. In a mouse model of type 2 diabetes, overfeeding led to greater cardiac accumulation of myristate-bearing ceramides, autophagy and cardiac hypertrophy compared with those seen in healthy controls. In a cell culture assay of cardiac hypertrophy, <i>CERS5</i> knockdown decreased cardiomyocyte hypertrophy, and <i>CERS5</i> overexpression or treatment with myristate worsened cardiomyocyte hypertrophy, compared with vehicle or vector treatment. Next steps include characterizing the effect of <i>Cers5</i> deletion on diabetic cardiomyopathy in mice.	Unpatented; licensing status not applicable	Russo, S.B. <i>et al. J. Clin. Invest.</i> ; published online Oct. 1, 2012; doi:10.1172/JCI63888 Contact: L. Ashley Cowart, Medical University of South Carolina, Charleston, S.C. e-mail: cowart@musc.edu
SciBX 5(41); doi:10.1038/scibx.2012.1086 Published online Oct. 18, 2012				

This week in therapeutics

Indication	Target/marker/pathway	Summary	Licensing status	Publication and contact information
Thyroid disease	NK2 homeobox 1 (NKX2-1; TTF1); paired box gene 8 (PAX8)	Studies in cell culture and in mice suggest embryonic stem cell (ESC)-derived follicular cells could be used to treat hypothyroidism. Transient Nkx2-1 and Pax8 overexpression in murine ESC culture led to differentiation into thyroid follicular cells, which organized into 3D follicular structures when treated with thyrotropin. In athyroid mice, thyroid follicular cells transplanted into the kidney capsule engrafted, developed into functional thyroid follicles and rescued thyroid homeostasis in eight out of nine mice. Next steps include developing a similar protocol using human stem cells and exploring ways to generate functional human thyroid tissue by reprogramming pluripotent stem cells derived from skin. SciBX 5(41); doi:10.1038/scibx.2012.1087 Published online Oct. 18, 2012	Unpatented; licensing status not applicable	Antonica, F. <i>et al. Nature</i> ; published online Oct. 10, 2012; doi:10.1038/nature11525 Contact: Sabine Costagliola, Free University of Brussels, Brussels, Belgium e-mail: scostag@ulb.ac.be
Infectious disease				
Viral hemorrhagic fever	Bas-Congo virus	Deep sequencing of patient samples suggests the Bas-Congo rhabdovirus could be a diagnostic marker for an acute viral hemorrhagic fever. In a serum sample taken from an acute patient, deep sequencing identified Bas-Congo virus RNA at a concentration of 1.09×10^6 copies/mL. Serum samples from the patient and an asymptomatic individual that cared for the patient contained high titers of neutralizing antibodies against the virus. Next steps could include screening for molecules that could inhibit replication of Bas-Congo rhabdovirus. SciBX 5(41); doi:10.1038/scibx.2012.1088 Published online Oct. 18, 2012	Patent and licensing status unavailable	Grard, G. <i>et al. PLoS Pathog.</i> ; published online Sept. 27, 2012; doi:10.1371/journal.ppat.1002924 Contact: Eric M. Leroy, International Center of Medical Research of Franceville, Franceville, Gabon e-mail: eric.leroy@ird.fr Contact: Charles Y. Chiu, University of California, San Francisco, Calif. e-mail: charles.chiu@ucsf.edu
Musculoskeletal disease				
Muscular atrophy; muscular dystrophy	Hexamethylene bis-acetamide inducible 1 (HEXIM1)	Mouse studies suggest inhibiting HEXIM1 signaling could help enhance muscle repair and regeneration. <i>Hexim1^{-/-}</i> mice had greater muscle regeneration following injury than wild-type controls. In wild-type mice, transplanted <i>Hexim1^{+/+}</i> satellite cells showed higher proliferative capacity and led to greater muscle regeneration than transplanted wild-type satellite cells. Next steps could include screening for compounds that reduce HEXIM1 signaling. SciBX 5(41); doi:10.1038/scibx.2012.1089 Published online Oct. 18, 2012	Patent and licensing status unavailable	Hong, P. <i>et al. J. Clin. Invest.</i> ; published online Oct. 1, 2012; doi:10.1172/JCI62818 Contact: M.A.Q. Siddiqui, SUNY Downstate Medical Center, Brooklyn, N.Y. e-mail: maq.siddiqui@downstate.edu
Neurology				
Alzheimer's disease (AD)	Glucagon-like peptide 1 (GLP-1)	Mouse studies suggest a GLP-1 cleavage product could help treat AD. In brain slices from an AD mouse model, pretreatment with the GLP-1 cleavage product GLP-1(9-36) ^{amide} restored hippocampal synaptic plasticity and normalized levels of mitochondria-derived superoxide, which is elevated by β -amyloid (A β). In a mouse model of AD, GLP-1(9-36) ^{amide} decreased learning and memory deficits compared with vehicle control without altering amyloid precursor protein (APP) or A β levels. Next steps could include testing GLP-1(9-36) ^{amide} in additional animal models of AD. SciBX 5(41); doi:10.1038/scibx.2012.1090 Published online Oct. 18, 2012	Patent and licensing status unavailable	Ma, T. <i>et al. J. Neurosci.</i> ; published online Oct. 3, 2012; doi:10.1523/JNEUROSCI.2107-12.2012 Contact: Eric Klann, New York University, New York, N.Y. e-mail: eklann@cns.nyu.edu

This week in therapeutics

Indication	Target/marker/pathway	Summary	Licensing status	Publication and contact information
Pain	Acid-sensing ion channel-1 (ASIC1); ASIC2	<p>Cell culture and mouse studies suggest snake venom-derived peptides that antagonize ASIC1 and ASIC2 could be useful for treating pain. In cell culture, mambalgins, a class of peptides isolated from black mamba venom, inhibited ASIC1 and ASIC2 signaling, whereas vehicle did not. In mice, mambalgin injection decreased response to painful stimuli with an effect comparable to that of morphine. Mambalgin-treated mice developed tolerance more slowly than morphine-treated mice and did not develop respiratory distress. Next steps include characterization of mambalgin peptides in other mouse models of pain.</p> <p>Theralpha S.A.S.'s THA904, a formulation of mambalgin, is in preclinical development to treat pain (<i>see Black mamba takes away pain, page 5</i>).</p> <p>SciBX 5(41); doi:10.1038/scibx.2012.1091 Published online Oct. 18, 2012</p>	Patented; licensed to Theralpha	<p>Diochot, S. <i>et al. Nature</i>; published online Oct. 3, 2012; doi:10.1038/nature11494 Contact: Anne Baron, Institute of Molecular and Cellular Pharmacology, Valbonne, France e-mail: anne.baron@ipmc.cnrs.fr Contact: Eric Lingueglia, same affiliation as above e-mail: lingueglia@ipmc.cnrs.fr</p>
Pain	Protease-activated receptor 2 (PAR2)	<p>Rodent studies suggest inhibiting PAR2 signaling could help treat cancer-associated pain. In mice, injection of supernatant from human squamous cell carcinomas induced acute mechanical allodynia in wild-type animals but not in <i>Par2</i>-deficient animals. In a mouse model of chemically induced squamous cell carcinoma in the mouth, a <i>Par2</i> deficiency led to complete absence of cancer-induced chronic allodynia. Next steps include developing a PAR2 antagonist.</p> <p>SciBX 5(41); doi:10.1038/scibx.2012.1092 Published online Oct. 18, 2012</p>	Unpatented; licensing status not applicable	<p>Lam, D.K. <i>et al. J. Neurosci.</i>; published online Oct. 10, 2012; doi:10.1523/JNEUROSCI.2399-12.2012 Contact: Brian L. Schmidt, New York University College of Dentistry, New York, N.Y. e-mail: bls322@nyu.edu</p>

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
Disease models			
Mouse model for nonalcoholic fatty liver disease	A mouse model of nonalcoholic fatty liver disease (NAFLD) could be used to help identify therapeutics. The I148M variant of <i>patatin-like phospholipase domain containing 3</i> (<i>PNPLA3</i> ; <i>ADPN</i>) is a risk factor for NAFLD. Mice that overexpressed the I148M variant of human <i>PNPLA3</i> in the liver had a fatty liver phenotype and showed other metabolic features of NAFLD. In these mice, liver secretions showed less hydrolysis and higher levels of disease-causing triacylglycerol than liver secretions from wild-type controls. Next steps could include using the model to evaluate therapeutic candidates.	Patent and licensing status unavailable	Li, J.Z. <i>et al. J. Clin. Invest.</i> ; published online Oct. 1, 2012; doi:10.1172/JCI65179 Contact: Helen H. Hobbs, The University of Texas Southwestern Medical Center, Dallas, Texas e-mail: helen.hobbs@utsouthwestern.edu
	SciBX 5(41); doi:10.1038/scibx.2012.1093 Published online Oct. 18, 2012		
Patient-specific cell culture model of cystic fibrosis (CF)	Human cell culture studies suggest <i>in vitro</i> -differentiated patient-derived stem cells could be useful for screening CF therapeutics. Patient-derived induced pluripotent stem (iPS) cells treated with a series of growth factors <i>in vitro</i> differentiated into airway epithelial cells. These cells expressed mutant <i>cystic fibrosis transmembrane conductance regulator</i> (<i>CFTR</i>) and showed lower ion flux than epithelial cells derived from healthy controls. Next steps include optimizing the differentiation procedure to improve yield and minimize generation of other cell types.	Unpatented; licensing status not applicable	Wong, A.P. <i>et al. Nat. Biotechnol.</i> ; published online Aug. 26, 2012; doi:10.1038/nbt.2328 Contact: James Ellis, The Hospital for Sick Children, Toronto, Ontario, Canada e-mail: jellis@sickkids.ca Contact: Janet Rossant, same affiliation as above e-mail: janet.rossant@sickkids.ca
	SciBX 5(41); doi:10.1038/scibx.2012.1094 Published online Oct. 18, 2012		
Drug delivery			
Liposomal formulation of saxitoxin and dexamethasone to delay neuropathic pain	Studies in rats suggest a liposomal formulation of the sodium channel blocker saxitoxin and the glucocorticoid agonist dexamethasone could delay neuropathic pain. In a spared nerve injury rat model, three sequential injections of the saxitoxin and dexamethasone liposomal formulations increased mechanical and thermal withdrawal threshold compared with no treatment. Next steps could include technically refining the method and testing the formulation in large animal studies.	Patent application filed; available for licensing	Shankarappa, S.A. <i>et al. Proc. Natl. Acad. Sci. USA</i> ; published online Oct. 8, 2012; doi:10.1073/pnas.1214634109 Contact: Daniel S. Kohane, Boston Children's Hospital and Harvard Medical School, Boston, Mass. e-mail: daniel.kohane@childrens.harvard.edu Contact: Robert Langer, Massachusetts Institute of Technology, Cambridge, Mass. e-mail: rlanger@mit.edu
	SciBX 5(41); doi:10.1038/scibx.2012.1095 Published online Oct. 18, 2012		
Drug platforms			
Improving drug-like properties of protein therapeutics through peptide extensions that interact with the Fc fragment of IgG receptor transporter- α (FCGRT; FCRN)	Peptide extensions that promote the interaction of proteins with FCRN could improve the drug-like properties of protein therapeutics. Some protein therapeutics are conjugated to the Fc domain of IgG, which interacts with FCRN, to increase plasma half-life, but the large size of the resulting fusion protein can interfere with tissue penetration and biological activity. In a proof-of-principle experiment, short peptide sequences that compete with IgG for binding to FCRN were conjugated to the N-terminal and/or C-terminal ends of a fluorescent protein. In cell culture, the peptide-based fusion proteins were internalized and transcytosed across a cell monolayer, which is similar to what is seen with IgG fusions. Next steps include testing peptide-modified protein therapeutics in animal models.	Patent application filed; available for licensing	Sokolosky, J.T. <i>et al. Proc. Natl. Acad. Sci. USA</i> ; Sept. 18, 2012; doi:10.1073/pnas.1208857109 Contact: Francis C. Szoka, University of California, San Francisco, Calif. e-mail: szoka@cgl.ucsf.edu
	SciBX 5(41); doi:10.1038/scibx.2012.1096 Published online Oct. 18, 2012		

This week in techniques

Approach	Summary	Licensing status	Publication and contact information
Mesoporous silica-coated upconversion fluorescent nanoparticles (UCNs) as a photodynamic therapy agent for cancer	<p>Mouse studies suggest UCNs could be photosensitizers that enable photodynamic therapy in deep tissue, which could be used to help treat cancer. UCNs were synthesized by coating NaYF₄-based nanoparticles with mesoporous silica, resulting in particles that emitted visible light in response to stimulation with deeper tissue-penetrating near-infrared light. In a mouse model of melanoma, intratumoral injection of UCNs conjugated to two photosensitizer dyes followed by near-infrared irradiation decreased tumor growth compared with intratumoral injection of vehicle with no irradiation. Next steps include additional preclinical efficacy studies in small and large animal models of cancer and preclinical toxicology studies.</p> <p>SciBX 5(41); doi:10.1038/scibx.2012.1097 Published online Oct. 18, 2012</p>	Patented; unavailable for licensing	<p>Idris, N.M. <i>et al. Nat. Med.</i>; published online Sept. 16, 2012; doi:10.1038/nm.2933 Contact: Yong Zhang, National University of Singapore, Singapore e-mail: biezy@nus.edu.sg</p>
Paper-based diagnostic for drug-associated hepatotoxicity	<p>A paper-based method for detecting liver enzymes in the blood could be useful for detecting drug-related hepatotoxicity in the point-of-care setting. The method consists of a paper-based microfluidic device that detects the liver enzymes aspartate aminotransferase (AST) and alanine aminotransferase (ALT) in a single drop of blood. In serum and whole-blood samples, the device generated colorimetric readouts that fell into one of three clinically relevant concentration ranges and showed over 90% accuracy. Next steps include testing the device in a third-world hospital setting in Vietnam.</p> <p>SciBX 5(41); doi:10.1038/scibx.2012.1098 Published online Oct. 18, 2012</p>	Findings patented; available for licensing from Diagnostics for All	<p>Pollack, N.R. <i>et al. Sci. Transl. Med.</i>; published online Sept. 19, 2012; doi:10.1126/scitranslmed.3003981 Contact: Jason P. Rolland, Diagnostics for All, Cambridge, Mass. e-mail: jrolland@dfa.org Contact: Nira R. Pollock, Beth Israel Deaconess Medical Center, Boston, Mass. e-mail: npollock@bidmc.harvard.edu</p>
Imaging			
Analysis of CT images to assess chronic obstructive pulmonary disease (COPD) phenotype	<p>Analysis of CT scans could be useful for assessing COPD phenotype. An image analysis technique called parametric response mapping was used to assess pulmonary CT scans from 194 patients with COPD. The analysis technique was used to determine disease severity and suggested functional small airways disease precedes emphysema in patients with COPD. Next steps include developing a software package to carry out parametric response map analysis of lung CT scans.</p> <p>SciBX 5(41); doi:10.1038/scibx.2012.1099 Published online Oct. 18, 2012</p>	Patent application filed covering methods and software required to perform parametric response map analysis of lung CT scans; licensed to Imbio LLC	<p>Galbán, C.J. <i>et al. Nat. Med.</i>; published online Oct. 7, 2012; doi:10.1038/nm.2971 Contact: Brian D. Ross, University of Michigan, Ann Arbor, Mich. e-mail: bdross@umich.edu</p>

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