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Liver X receptor marks the spot

By Lev Osherovich, Senior Writer

Multiple companies have shelved liver X receptor agonists for cardiovascular indications because of unfavorable effects on lipid levels. Now, a New York team and **Rgenix Inc.** have found a different role for the agonists in metastatic melanoma.¹

The group, led by **The Rockefeller University** assistant professor Sohail Tavazoie, came upon the nuclear hormone receptor as a melanoma target while studying the effect of apolipoprotein E (APOE) on cancer metastasis.

APOE is the protein component of cholesterol-carrying lipoprotein particles.

In 2012, Tavazoie's team discovered that Apoe produced by noncancerous tissue combats melanoma vascularization and metastasis.²

"In our previous paper we used an unbiased approach to show that Apoe suppresses metastasis of melanoma cells," said Tavazoie. The tricky part, he said, was figuring out how to elevate Apoe levels.

In the new study, Tavazoie's team tested the hypothesis that liver X receptor (LXR) agonists, which are known to increase APOE levels, would have a beneficial effect in melanoma.

"The idea was to use the cell's machinery to make more APOE in the stroma," said Tavazoie.

The findings present repurposing opportunities for shelved LXR agonists, including tool compounds originally developed by **GlaxoSmithKline plc** and Tularik Inc., which was acquired by **Amgen Inc.** in 2004.

Those compounds hit both isotypes of LXR—LXR- β (NR1H2) and LXR- α (NR1H3)—as well as the related retinoid X receptor (RXR). The molecules raised triglyceride levels in rodents and did not advance into clinical development.

Metastasis stasis

Tavazoie's team used tool compounds and a variety of cell culture and mouse models to make the case for agonizing LXR- β to treat melanoma.

In vitro, nonselective LXR agonists prevented invasion and endothelial

"Zelboraf and Yervoy work in about half of patients, but with our APOE activation therapy, there is response across all tumor types, even tumors that have developed resistance to targeted therapies."

—Sohail Tavazoie,
The Rockefeller University

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recruitment, two key traits of metastatic tumors. In several mouse models of melanoma, oral LXR agonists prevented metastasis to the brain and lung and increased survival compared with vehicle controls.

“When we fed mice with these drugs, we found that they strongly suppressed melanoma growth and metastasis,” said Tavazoie. “We see 30-fold reductions in metastasis.”

shRNA knockdown or antibody depletion of APOE blocked the beneficial effects of LXR agonists, indicating that the treatment likely worked by inducing the expression of APOE.

The team then used genetics to determine that somatic LXR- β was the key target for preventing melanoma metastasis.

In *Lxr- β* knockout mice, tumors did not respond to nonselective LXR agonists. Mice lacking *Lxr- α* responded comparably to wild-type mice with tumors. Thus, the team concluded that activation of LXR- β but not LXR- α in normal tissue surrounding a tumor could combat metastasis.

Tavazoie thinks that raising APOE levels with LXR- β agonists is an attractive option for melanomas as an adjunct to targeted therapies that directly block tumor cell division.

Marketed melanoma therapies include Zelboraf vemurafenib, a selective BRAF inhibitor from **Roche, Chugai Pharmaceutical Co. Ltd.** and **Daiichi Sankyo Co. Ltd.**, and Yervoy ipilimumab, a human mAb against CTLA-4 (CD152) from **Bristol-Myers Squibb Co.**

Indeed, the team found that a combination of LXR agonists with Zelboraf or a CTLA-4 antibody enhanced the drugs' effects on tumor metastasis and increased survival in mice compared with Zelboraf or CTLA-4 antibody alone. The combination also worked in mice with tumors resistant to Zelboraf.

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“Zelboraf and Yervoy work in about half of patients, but with our APOE activation therapy, there is response across all tumor types, even tumors that have developed resistance to targeted therapies,” said Tavazoie, who is also cofounder and chair of the scientific advisory board at Rgenix.

Results were reported in *Cell* and are covered by pending patents licensed to Rgenix.

LXR revival

The challenge to using LXR agonists in melanoma is getting selectivity for LXR- β while avoiding cardiovascular liabilities.

Rgenix CEO David Darst said that the company in-licensed a portfolio of patents late last year from an undisclosed pharma covering composition of matter for a family of LXR agonists.

“Our lead candidate is chemically related to one of the compounds used in the paper” but has undergone optimization to improve its selectivity for LXR- β , said Darst. “We’re in the process of conducting a dose range-finding toxicity study in monkeys.”

Darst said that the company plans to be in the clinic by the first half of 2015.

At least one other company—**Vitae Pharmaceuticals Inc.**—has LXR- β -selective compounds in development. Vitae’s compounds are in preclinical testing for atherosclerosis and atopic dermatitis. CSO Richard Gregg said that Vitae’s LXR agonists are highly selective for LXR- β and thus have a more favorable effect on lipid levels than pan-LXR agonists.

“LXR has been around as a target for a long time, about 10 years or so, but there have been certain problems of selectivity and lipid elevation,” said Gregg. “I don’t believe there are many active programs going on right now. People have largely dropped out of this space.”

Tavazoie’s study suggests that LXR agonists could “have a very positive impact, inhibiting growth and metastasis” of melanoma, said Gregg. “The downside is that LXR agonists have a tendency to induce lipid synthesis,

leading to increased circulating triglycerides and fat accumulation in the liver.”

“For atherosclerosis, this is a big downside, but for tumors these side effects are better accepted,” said Gregg. “If a cancer is going to kill you in six months, elevated triglycerides are not as much of a concern.”

Tavazoie said that the lipid-altering effects of LXR agonists are transient.

“Previous compounds have been shown to cause an acute increase in levels of triglycerides, but this goes away,” said Tavazoie. “This should not be a concern for melanoma patients.”

Rgenix was formed in 2010 to develop therapies for metastatic cancer coming out of Tavazoie’s lab. The company also has mAbs for triple-negative breast cancer, including an antibody that targets insulin-like growth factor binding protein 2 (IGFBP2). Rgenix hopes to partner its mAbs and is focused on internal development of its small molecules.

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Heart cells: no longer undivided

By Michael J. Haas, Senior Writer

The inability of adult heart cells to divide rapidly enough to repair cardiac damage has been a major impediment to regenerating heart tissue and preventing fibrosis after myocardial infarction. Now, a U.S. team has used *cyclin A2* gene therapy to induce cardiomyocyte division and improve heart function in pig models of myocardial infarction.¹

The technology has been licensed to **VentriNova Inc.**, which is planning IND-enabling studies and is seeking investors to fund clinical testing of *cyclin A2* (*CCNA2*) gene therapy to treat MI.

Most mammalian cells regenerate their tissues after injury by undergoing mitosis, but cardiomyocytes do not. Instead, cardiac fibroblasts proliferate after MI. Although they replace the damaged tissue and thus maintain the organ's structural integrity,^{2,3} they result in fibrotic scarring that compromises heart function and can lead to heart failure.

In the 1990s, studies by multiple groups showed that *CCNA2* regulated the cell cycle transitions required for mitosis in many mammalian cell types^{4,5} but was silenced in mammalian cardiomyocytes shortly after birth.⁶ Clinical studies have shown that cardiomyocytes undergo a limited degree of turnover—a process by which mitotic cells replace older ones—across the human lifespan.^{7,8}

The unanswered question was whether *CCNA2* in adult cardiomyocytes could be reactivated to regenerate heart tissue.

Answers started to emerge in 2004, when a group led by

Debra Wolgemuth at **Columbia University Medical Center** engineered mouse embryos to keep *Ccna2* active in the heart after birth. The team observed significant cardiomyocyte mitosis in the postnatal mice well into adulthood.⁹

These findings led Hina Chaudhry, a postdoctoral fellow in Wolgemuth's group and first author on the mouse study, to investigate whether cardiomyocytes in the engineered mice could repair heart damage after MI.

Three years later, Chaudhry showed that the engineered mice regenerated heart tissue through cardiomyocyte mitosis.¹⁰ Subsequently, another team led by Chaudhry showed that in wild-type rat models of MI, an adenoviral vector encoding mouse *Ccna2* increased cardiac function and the density of heart muscle tissue and decreased cardiac fibrosis compared with empty vector.¹¹

Wolgemuth is a professor of genetics and development at the Columbia University Medical Center. Chaudhry is now an associate professor of medicine and director of cardiovascular regenerative medicine at the **Icahn School of Medicine at Mount Sinai**.

For the current study, Chaudhry's team at Mount Sinai—along with a researcher from the **University of Washington Medical Center**—tested the *Ccna2* gene therapy in pig models of MI, which are more clinically relevant than murine species in terms of both size and cardiac genetics.

In the pigs, injection of the adenoviral vector encoding murine *Ccna2* into cardiac tissue near the infarct site increased ejection fraction—a measure of cardiac function—at six weeks after treatment compared with baseline. The gene therapy also decreased cardiac fibrosis and increased the number of actively dividing cardiomyocytes compared with empty vector.

Next, the team examined heart tissue from the treated and control

Table 1. Cardiovascular expressions. At least 10 companies have gene therapies in preclinical through Phase III development to treat a range of cardiovascular indications. The majority of the gene therapies act by promoting angiogenesis or improving the function of existing heart cells. Only one therapy—VN-100 from VentriNova Inc.—regenerates heart tissue by promoting the proliferation of existing cardiomyocytes.

Source: BCIQ: BioCentury Online Intelligence

Company	Product	Description	Indication(s)	Status
Cardium Therapeutics Inc. (OTCQB:CRXM)	Generx alferminogene tadenovec (Ad5FGF4)	Adenoviral vector encoding <i>fibroblast growth factor 4</i> (<i>FGF4</i>)	Coronary artery disease (CAD); ischemia/reperfusion injury	Phase III
Vical Inc. (NASDAQ:VICL); AnGes MG Inc. (Tokyo:4563); Daiichi Sankyo Co. Ltd. (Tokyo:4568); Mitsubishi Tanabe Pharma Corp. (Tokyo:4508)	Collatogene beperminogene perplasmid (AMG0001; HGF gene therapy)	Plasmid encoding human <i>hepatocyte growth factor/scatter factor</i> (<i>HGF/SF</i>)	Advanced peripheral artery disease (PAD); ischemia/reperfusion injury	Phase III
Celladon Corp. (NASDAQ:CLDN); AmpliPhi Biosciences Corp. (OTCBB:APHB)	Mydicar (AAV1/SERCA2a)	Recombinant adeno-associated viral (AAV) vector encoding <i>ATPase Ca⁺⁺ transporting cardiac muscle slow twitch 2</i> (<i>ATP2A2</i> ; <i>SERCA2A</i>)	Heart failure Advanced heart failure in patients with a left ventricular assist device (LVAD); diastolic heart failure; pulmonary arterial hypertension (PAH); arteriovenous fistula maturation failure in dialysis patients	Phase IIb Preclinical
ViroMed Co. Ltd. (KOSDAQ:084990)	VM202	Proprietary pCK vector encoding engineered <i>HGF/SF</i>	Ischemia/reperfusion injury CAD	Phase II Phase I/II
VentriNova Inc.	VN-100	Adenoviral vector encoding <i>cyclin A2</i> (<i>CCNA2</i>)	Myocardial infarction (MI)	Preclinical
NanoCor Therapeutics Inc.	Carfostin	<i>Protein phosphatase 1 regulatory inhibitor subunit 1A</i> (<i>PPP1R1A</i>) delivered via biological nanoparticle technology	Congestive heart failure (CHF)	Preclinical

models for markers of stem cells or cardiac progenitor cells and found no differences between the two groups of animals. This indicated that the new cardiomyocytes in the treated models did not arise from stem or progenitor cells that had been recruited to the infarct site.

Lastly, video imaging experiments in primary pig cardiomyocytes confirmed that the *Ccna2* gene therapy induced mitosis.

Taken together, the findings showed that *CCNA2* gene therapy could regenerate heart tissue and prevent fibrosis after MI by inducing existing cardiomyocytes to divide and repair the damage, the team wrote in its report in *Science Translational Medicine*.

“This study addresses what I think is the most important question in cardiovascular medicine: can we get cardiomyocytes to divide?” said Chaudhry, who founded VentriNova in 2006 to develop the *CCNA2*-based technology.

The *CCNA2* gene therapy could be more effective at treating

MI than stem cell-based therapies, most of which have not resulted in significant or lasting improvements in cardiac function or shown evidence that the stem cells differentiated into cardiomyocytes, she said.

Chaudhry said that **Columbia University** holds a portfolio of patents—including at least three

of which are issued—covering the *CCNA2* gene therapy technology and its therapeutic applications, and Columbia has licensed the IP to VentriNova.

At least nine other companies have gene therapies in preclinical and clinical development to treat a range of cardiovascular indications, although none is intended to regenerate cardiac tissue and prevent fibrosis after MI (see Table 1, “Cardiovascular expressions”).

Division of labor

VentriNova plans to examine tissue samples from the *Science Translational Medicine* study for any signs of *Ccna2* activation in noncardiac tissues. Chaudhry does not expect to find any such signs

because the adenoviral vector is replication deficient and thus cannot spread beyond the first cells it transfects.

Moreover, “we did not find evidence of *Ccna2* activation in noncardiomyocyte cells, even within the heart tissue” of the pig models, she said.

Nevertheless, VentriNova has developed an adenoviral vector encoding human *CCNA2* and a cardiac-specific promoter to avoid the potential for *CCNA2* activation in noncardiac tissues, she said.

The company plans to begin IND-enabling studies of that product—VN-100—in pig models of MI this year.

VentriNova is seeking investors for a series A round that would fund clinical development of the technology, Chaudhry said.

She added that her Mount Sinai team expects to publish a paper this year describing the mechanisms by which *CCNA2* becomes silent after birth.

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“This study addresses what I think is the most important question in cardiovascular medicine: can we get cardiomyocytes to divide?”

—Hina Chaudhry,

Icahn School of Medicine at Mount Sinai

Depending on SWI/SNF

By Chris Cain, Senior Writer

Gain-of-function alterations in histone-modifying proteins drive multiple cancers and are now being targeted by compounds in the clinic,¹ but loss-of-function mutations, which are more frequently found in chromatin remodelers, remain largely intractable. Separate teams from Japan, Boston and **Novartis AG** now have identified synthetic lethal interactions that could be exploited to help treat cancers with mutations in the SWI/SNF chromatin-remodeling complex.²⁻⁵

The key question is whether these targets—core regulatory proteins within the SWI/SNF (switch/sucrose nonfermentable) complex—can be selectively inhibited with an acceptable therapeutic index.

SWI/SNF is a large multiprotein complex that plays diverse roles in regulating transcription and DNA replication and repair by altering chromatin structure. Loss-of-function mutations in members of the complex have been found in several tumor types.

At the [SciBX Summit on Innovation in Drug Discovery and Development](#) last October, Charles Roberts said that these mutations were ripe for further functional exploration.

“Eight different subunits of this complex are currently mutated in cancer at quite high frequencies—the latest data suggest that at least 20% of all human cancers have a mutation of one or another SWI/SNF subunit. Further, the genes encoding these subunits are being validated as bona fide tumor suppressors using mouse models. Now, an important question is, what can we do about it therapeutically?” asked Roberts, who is an associate professor of pediatrics at **Harvard Medical School** and an associate professor of pediatric oncology at the **Dana-Farber Cancer Institute**.

Initial work suggested that uncovering new genetic dependencies in SWI/SNF-mutant cancers could point the way to actionable targets. For example, mutations in the SWI/SNF subunit *SNF5* (*SWI/SNF-related matrix-associated actin-dependent regulator of chromatin subfamily b member 1; SMARCB1*) cause the rare pediatric cancer malignant rhabdoid sarcoma. Studies from Roberts^{6,7} and cancer epigenetics company **Epizyme Inc.**⁸ showed that these cancers require BRG1 (*SWI/SNF-related matrix-associated actin-dependent regulator of chromatin subfamily a member 4; SMARCA4*) and EZH2 (*enhancer of zeste homolog 2*) function.

BRG1 knockdown or EZH2 inhibition killed *SNF5*-mutant malignant rhabdoid sarcoma cells. Epizyme’s EZH2 inhibitor E7438 is in Phase I/II trials to treat lymphoma.

However, *SNF5* is only one of many SWI/SNF complex components mutated in cancer. The dependencies created by mutations in other subunits remained unknown.

Now, three separate teams including Roberts’ have shown that loss-of-function mutations in *BRG1* cause cells to become dependent on the highly related SWI/SNF component BRM (*SMARCA2*).²⁻⁴

An additional study also by Roberts’ group homed in on mutations in the SWI/SNF complex member AT rich interactive domain 1A (*ARID1A*) and showed that cells with the mutation became dependent on the closely related protein *ARID1B*.⁵

BRGing in

The teams took distinct approaches to arrive at the same conclusion, namely, that BRM is required for viability in tumors with mutations in *BRG1*.

The first team to publish its results was led by Takashi Kohno, chief of the Division of Genome Biology at Japan’s **National Cancer Center Research Institute**. Because BRM and *BRG1* are highly homologous and play complementary roles, the group sought to test whether depletion of BRM might be synthetically lethal in *BRG1*-mutant cell lines.

Indeed, in a panel of *BRG1*-mutant non-small cell lung cancer (NSCLC) cell lines, siRNA against *BRM* significantly decreased viability compared with control siRNA, whereas *BRG1*-intact cells were unaffected.

Adding back wild-type *BRG1* restored viability, whereas adding back a catalytically inactive mutant form of *BRG1* did not. In a xenograft model of *BRG1*-mutant NSCLC, depletion of BRM decreased tumor volume compared with no depletion. Results were published in *Cancer Research*.⁴

A second study published in January by Roberts in collaboration with researchers at the **Broad Institute of MIT and Harvard** took an unbiased approach using Project Achilles, a genome-wide shRNA screening effort using genetically defined cancer cell lines.

When 8 cell lines with unambiguous inactivating alterations in *BRG1* were compared to the remaining 157 cell lines, *BRM* emerged as the top essential gene. Results were published in *Molecular and Cellular Biology*.³

In a separate analysis of the Project Achilles data published in *Nature Medicine*, Roberts’ lab also showed that mutations in another SWI/SNF complex member, *ARID1A*, sensitized cells to depletion of *ARID1B*.⁵

Finally, a publication on BRM dependency from a team led by Frank Stegmeier and Zainab Jagani at the **Novartis Institutes for BioMedical Research** (NIBR) described a high-coverage shRNA screen of chromatin regulators that pinpointed *BRM* as an essential gene in *BRG1*-mutant cancers. Results were published in the *Proceedings of the National Academy of Sciences*.²

Both Roberts’ and Stegmeier’s teams showed that knockdown of *BRM* did not completely disrupt the SWI/SNF complex. That finding suggested that the activity of the BRM-containing SWI/SNF complex was responsible for the oncogenic effects caused by the *BRG1* mutations.

Stegmeier is director and head of Cambridge oncology target ID and validation at NIBR. Jagani is an investigator at NIBR.

The Novartis and Boston academic teams operated independently, although the teams communicated results before publication, and Jagani and Roberts are authors on each other’s papers.

“From these findings it is still a long way to go to a potentially successful therapy. It is not yet clear if one can engineer selectivity into small molecules inhibiting the ATPase domain of BRM and BRG1. The same question arises when considering drugging the BRM and BRG1 bromodomains.”

—Patrick Trojer,
Constellation Pharmaceuticals Inc.

Chemical matters

The series of studies collectively makes the case for inhibiting BRM in the genetically defined subset of BRG1-mutant cancers. However, only one inhibitor of the target has been disclosed, and the molecule is nonselective. Thus, the safety of the approach remains an open question.

Roberts told *SciBX*, “A key question is whether there is a therapeutic window we can take advantage of.”

Central to evaluating the therapeutic window will be the development of chemical matter that can selectively inhibit BRM or BRG1. The proteins consist of two potentially druggable domains: an ATPase domain required for chromatin remodeling and a bromodomain that binds to acetylated histone tails.

The **Structural Genomics Consortium** has developed a probe in collaboration with **Pfizer Inc.** The molecule, dubbed PFI-3, inhibits the bromodomains of BRM, BRG1 and polybromo 1 (PBRM1; PB1). Although the chemical properties of the compound are available on SGC’s [website](#), no studies detailing the function of the molecule have been published.

Stefan Knapp, a professor of structural biology at the **University of Oxford** and principal investigator of epigenetics chemical biology at SGC, told *SciBX* that the inhibitor has not yet been published because finding a biological effect has been challenging.

“The SWI/SNF complex contains many bromodomains, and predicting the outcome of chemical inhibition of a few of them is challenging. There is no effect of the inhibitor on cell proliferation, but we now see interesting phenotypes in developmental models. We hope that we will publish these data soon,” said Knapp.

He added that, based on these findings, he does not expect that BRG1 or BRM bromodomain inhibitors would show the same effect as *BRM* knockdown experiments.

Patrick Trojer, senior director and head of biology at epigenetics company **Constellation Pharmaceuticals Inc.**, said that it is still the early days when evaluating BRG1 and BRM as drug targets. “From these findings it is still a long way to go to a potentially successful therapy. It is not yet clear if one can engineer selectivity into small molecules inhibiting the ATPase domain of BRM and BRG1. The same question arises when considering drugging the BRM and BRG1 bromodomains,” said Trojer.

He added, “It seems clear that inhibition of both BRM and BRG1 ATPase domains will be quite toxic and needs to be avoided. In general, ATPases have been difficult to drug and perhaps do not lend themselves to identifying potent small molecule inhibitors. But it is biological data like these that will get drug discoverers excited and perhaps initiate certain efforts to find out.”

Stegmeier agreed that “additional studies are required to fully understand which domains and functions of BRM are critical for cancer dependency.” He declined to disclose if Novartis is developing inhibitors of SWI/SNF complex members or whether any IP has been filed around this work.

Kohno and Roberts also did not disclose the IP status of their work.

Stegmeier said that future studies will focus on understanding the function of residual SWI/SNF complex activity in the mutant cancers and said that placing context around the role of the mutations will be important.

“Inactivating mutations in *SWI/SNF* co-occur in the context of other genetic lesions, and current models of inactivation are restricted to complete gene knockout in mouse models, making it difficult to clearly predict oncogenic effects as well as safety concerns,” he said. “Such parameters would therefore have to be carefully studied and may differ depending on the mechanism of action of pharmacological inhibitors.”

Roberts is further studying the role of residual SWI/SNF complex activity and did not disclose plans for development of inhibitors of BRG1, BRM or ARID1B. The last of the three targets could be the hardest to inhibit because it would require blocking protein-protein interactions.

Trojer wants to see additional studies elucidating the function of ARID1A and B in greater detail. He also noted that the PBRM1 subunit of the SWI/SNF complex is frequently mutated in cancer as well, so it would be interesting to look for synthetic lethal dependencies in *PBRM1*-mutant cells.

Trojer did not disclose whether Constellation is pursuing the targets.

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COMPANIES AND INSTITUTIONS MENTIONED

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Taking TIMP3 to heart

By Lauren Martz, Staff Writer

A U.S. team has found a way to harness the cardioprotective activity of tissue inhibitor of metalloproteinases 3 while avoiding its off-target effects by embedding it in a hydrogel for direct injection into the heart.¹ Although preclinical data show that local delivery of the molecule could help prevent heart failure after myocardial infarction in patients with ventricular dilation, it may have a detrimental effect in other patients, making patient selection critical.

After myocardial infarction (MI), left ventricular wall damage is partly caused by overactive matrix metalloproteinase (MMP) enzymes that break down extracellular matrix in the ischemic tissue.

Under normal conditions, tissue inhibitors of metalloproteinases (TIMPs) control MMP activity and help regulate the breakdown of matrix proteins. After MI, however, there is an increase in MMP plasma levels without a matching change in levels of TIMPs, creating an imbalance in MMP regulation.

The unchecked proteolysis causes thinning of the left ventricle wall, dilation and eventual loss of structural support—termed left ventricular remodeling—which leads to heart failure.

Previous clinical studies have tested various MMP inhibitors.² However, according to Merry Lindsey, problems in achieving proper doses and side effects of systemic administration of MMP inhibitors have prevented clinical use.

Lindsey is director of **The University of Mississippi Medical Center's** Jackson Center for Heart Research, a professor of physiology and biophysics at the University of Mississippi Medical Center and director of the **San Antonio Cardiovascular Proteomics Center** at **The University of Texas Health Science Center at San Antonio**.

Tissue inhibitor of metalloproteinases 3 (TIMP3) was pegged as a key player in the heart in 2009 when knockout studies in mice showed that eliminating *Timp3* causes adverse ventricular remodeling and accelerates heart failure.³

To find a therapeutic strategy that can block MMP activity in patients, Francis Spinale and colleagues decided to test whether increasing TIMP3 levels exclusively in the heart via a slow-release delivery system could improve cardiac recovery following MI without incurring effects in other organs.

Spinale is a professor of cell biology and anatomy at the **University of South Carolina School of Medicine**. The study also included researchers from the **University of Pennsylvania** and **Amgen Inc.**

Straight to the heart

The team encapsulated recombinant TIMP3 (rTIMP3) in a biodegradable hyaluronic acid gel and obtained slow release of rTIMP3 *in vitro* that maintained a uniform release profile for at least 14 days.

The hydrogel also produced the desired kinetics *in vivo*. In pigs, rTIMP3 hydrogels remained at the left ventricular injection site for at least seven

days after injection. No rTIMP3 was detected in the liver, kidneys, lungs or blood.

In a pig model of MI, rTIMP3 hydrogel injection into the left ventricle decreased left ventricle dilation, wall stress and regional infarct expansion and partially increased left ventricle wall thickness compared with injection of saline or unloaded hydrogels.

rTIMP3 hydrogel-treated pigs had lower pulmonary capillary wedge pressure than saline- or unloaded gel-treated pigs, indicating a decreased risk of progression to heart failure.

The team also showed that rTIMP3 decreased inflammatory markers and increased collagen content in left ventricular myocardial cells compared with saline or unloaded hydrogels.

Because some hydrogels without embedded therapeutics have been used to affect infarct expansion,⁴ the team showed that most of the effects were caused by rTIMP3 and not the gel by boiling the protein to destroy its activity. Boiled rTIMP3-loaded hydrogels lacked cardioprotective effects.

Together, the data suggest that TIMP3 acts as a cardioprotective agent after MI by stabilizing the extracellular matrix to improve left ventricular structure and by dampening the MI-associated inflammation.

Data were published in *Science Translational Medicine*.

LoneStar Heart Inc. has Algisyl-LVR, a hydrogel injected into the left ventricle wall during surgery, in Phase II/III testing for heart failure. The company is also developing a minimally invasive version of the hydrogel for catheter-based delivery, which is in preclinical development.

Ventrix Inc. has the injectable hydrogel VentiGel in preclinical testing for congestive heart failure.

“Using the hydrogel delivery system was an ingenious way to localize the sustained release of TIMP3 to the site of MI.”

—Merry Lindsey,
*The University of Mississippi
Medical Center*

Local hero

According to Lindsey, the localized hydrogel delivery system should minimize the risk of off-target effects.

“Using the hydrogel delivery system was an ingenious way to localize the sustained release of TIMP3 to the site of MI,” she said.

Patrick Hsieh, David Lundy and Yi-Dong Lin told *SciBX* that although many other approaches have focused on delivery of growth factors, extracellular matrix proteins or living cells to the infarct area, “the main advantage of the recombinant TIMP3 approach is the direct targeting of the left ventricular remodeling by MMPs, caused by the MMP/TIMP3 imbalance responsible for progression to heart failure after MI.”

However, they added that confining the gel to the damaged area will be important because if it spreads to neighboring healthy regions, it could weaken the tissue and cause side effects. Previous attempts to inject substances into the heart have run into problems with insufficient retention within the area or inadequate release beyond the immediate injection site.

Hsieh is a joint associate research fellow at **Academia Sinica's** Institute of Biomedical Sciences. Lundy and Lin are postdoctoral fellows at Academia Sinica.

Nikolaos Frangogiannis told *SciBX* that the delivery timing will need to be optimized.

“Infarct healing is a dynamic process. There is a window of therapeutic opportunity—if this is missed, then the result of an intervention may be detrimental.”

Frangogiannis is a professor of medicine and chair in cardiovascular medicine at the **Albert Einstein College of Medicine of Yeshiva University**.

The Academia Sinica team added that although there is extensive remodeling during the first two weeks, those processes continue for at least two months after MI.

Lindsey said that because the results came from injections given at the time of MI, it will be necessary to see the effect of rTIMP3 given after the heart has undergone some irreversible ischemic injury. This would indicate whether TIMP3 can reverse and not just prevent the adverse remodeling.

Patient benefits

Florence Pinet told *SciBX* that current treatments—which include acute reperfusion strategies and anti-remodeling medications such as angiotensin-converting enzyme (ACE) inhibitors and β -blockers—do not prevent ventricle remodeling in about 30% of patients.

Pinet is research director at the **Institut National de la Sante et de la Recherche Medicale (INSERM) UMR744**.

However, selecting the right patient population could be difficult.

According to Frangogiannis, clinical heart failure is often associated with ventricular dilation and dysfunction, and patients with large infarcts might benefit from the rTIMP3 hydrogels.

One problem, he said, is that not all heart attack patients develop dilation following infarction, and some patients develop heart failure without dilation. In the latter, heart failure can be caused by overactive matrix deposition leading to formation of a stiff scar and diastolic heart failure.

“The therapy proposed here may be effective for patients with a defect in scar formation that tend to exhibit dilation of the heart following infarction but not for other groups with different physiological responses.” He added that patients with overactive fibrotic responses may be negatively affected by the treatment because of the increase in collagen deposition that results.

Imaging or biomarker approaches could help select for patients at high risk of dilative responses, he said.

Another issue, said Frangogiannis, is that most MI patients do not

require surgery and are treated with percutaneous interventions or pharmacologic therapies for rapid reperfusion.

“Development of a catheter-based strategy to deliver the hydrogel-TIMP3 would be a major step forward,” he said.

Frangogiannis added that although the post-MI group would be best suited for the rTIMP3 hydrogels, the gels may also help patients with chronic heart failure who exhibit progressive dilative remodeling.

Spinale told *SciBX* that an undisclosed entity has filed a patent application covering the use of rTIMP3 hydrogels in arthritis, vascular inflammation, heart failure and related diseases. The IP is unlicensed and currently unavailable for licensing.

Martz, L. *SciBX* 7(9); doi:10.1038/scibx.2014.246
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The University of Mississippi Medical Center, Jackson, Miss.

University of Pennsylvania, Philadelphia, Pa.

University of South Carolina School of Medicine, Columbia, S.C.

The University of Texas Health Science Center at San Antonio, San Antonio, Texas

Ventrix Inc., San Diego, Calif.

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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
Autoimmune disease				
Autoimmune disease	Integrin α_9	<i>In vitro</i> and mouse studies suggest inhibiting integrin α_9 could help treat autoimmune diseases. In mice treated with an adjuvant that expands lymph nodes, an anti-integrin α_9 antibody increased draining lymph node size and CD4 ⁺ T cell and CD19 ⁺ B cell numbers and decreased lymphocyte egress from the lymph nodes compared with IgG control. In a mouse experimental autoimmune encephalomyelitis (EAE) model, prophylactic injection of the anti-integrin α_9 antibody decreased symptom severity, immune cell infiltration into the spinal cord and demyelination compared with IgG control injection. Next steps could include testing whether the antibody blocks integrin α_9 -induced secretion of sphingosine 1-phosphate (S1P) from lymphatic endothelial cells <i>in vitro</i> and <i>in vivo</i> .	Patent application filed; licensing status undisclosed	Ito, K. <i>et al. Proc. Natl. Acad. Sci. USA</i> ; published online Feb. 10, 2014; doi:10.1073/pnas.1311022111 Contact: Toshimitsu Uede, Hokkaido University, Sapporo, Japan e-mail: uedetoshimitsu@icloud.com Contact: Koyu Ito, same affiliation as above e-mail: ito@igm.hokudai.ac.jp
SciBX 7(9); doi:10.1038/scibx.2014.247 Published online March 6, 2014				
Cancer				
Bladder cancer	Phosphoinositide 3-kinase catalytic subunit α -polypeptide (PIK3CA; p110 α); protein kinase B (PKB; AKT3); fibroblast growth factor receptor 3 (FGFR3; CD333); HER2 (EGFR2; ErbB2; neu); epidermal growth factor receptor 3 (EGFR3; HER3; ErbB3)	Genomic studies suggest antagonists of PIK3CA, AKT3, FGFR3, HER2 or HER3 could be useful for treating bladder cancer. Whole-genome and RNA sequencing of 131 urothelial bladder cancer biopsies identified activating mutations or amplifications in the above targets or related pathways in approximately 69% of tumors. Next steps could include classifying patient tumors based on mutations and testing mutation-matched inhibitors <i>in vitro</i> and in animal models. At least 60 products are marketed or in development that target these proteins to treat a range of tumor types.	Patent and licensing status undisclosed	The Cancer Genome Atlas Research Network. <i>Nature</i> ; published online Jan. 29, 2014; doi:10.1038/nature12965 Contact: John N. Weinstein, The University of Texas MD Anderson Cancer Center, Houston, Texas e-mail: jweinste@mdanderson.org
SciBX 7(9); doi:10.1038/scibx.2014.248 Published online March 6, 2014				
Cancer	AT rich interactive domain 1A (ARID1A); ARID1B	Cell culture studies suggest inhibiting <i>ARID1B</i> could help treat cancers with <i>ARID1A</i> mutations. ARID1A and B are 60% identical and regulate chromatin remodeling as part of the SWI/SNF complex. Mutations in <i>ARID1A</i> have been previously identified in a variety of tumor types. In multiple <i>ARID1A</i> -mutant cancer cell lines, <i>ARID1B</i> -targeting shRNA decreased cell growth compared with control shRNA, leading to the degradation of the SWI/SNF chromatin remodeling complex. Next steps could include designing inhibitors of ARID1B (<i>see Depending on SWI/SNF, page 6</i>).	Patent and licensing status unavailable	Helming, K.C. <i>et al. Nat. Med.</i> ; published online Feb. 23, 2014; doi:10.1038/nm.3480 Contact: Charles W.M. Roberts, Dana-Farber Cancer Institute, Boston, Mass. e-mail: charles_roberts@dfci.harvard.edu
SciBX 7(9); doi:10.1038/scibx.2014.249 Published online March 6, 2014				

This week in therapeutics (continued)

Indication	Target/marker/pathway	Summary	Licensing status	Publication and contact information
Cancer	Not applicable	<p>A study in cell culture suggests a conjugate prodrug of cisplatin and aspirin could be useful for reducing inflammation associated with chemotherapy. In one cultured human prostate cancer cell line, the conjugate increased apoptosis compared with a nonconjugated combination of the two compounds. In cultured macrophages, the conjugate decreased production of the proinflammatory cytokines IL-6 and tumor necrosis factor-α (TNF-α) and increased levels of the anti-inflammatory cytokine IL-10 compared with the nonconjugated combination. Next steps include optimization and preclinical testing in animal models of cancer.</p> <p>SciBX 7(9); doi:10.1038/scibx.2014.250 Published online March 6, 2014</p>	Patent pending; licensed to Partikula LLC	<p>Pathak, R.K. <i>et al. Angew. Chem. Int. Ed.</i>; published online Jan. 22, 2014; doi:10.1002/anie.201308899 Contact: Shanta Dhar, The University of Georgia, Athens, Ga. e-mail: shanta@uga.edu</p>
Cancer	SWI/SNF-related matrix-associated actin-dependent regulator of chromatin subfamily a member 2 (SMARCA2; BRM); SMARCA4 (BRG1)	<p>Cell culture and mouse studies suggest inhibiting BRM could help treat <i>BRG1</i>-mutant cancers. BRM and BRG1 are related ATP-dependent chromatin remodeling proteins. An shRNA library targeting chromatin regulators was screened across a panel of cancer cell lines, and BRM was found to be essential for growth of <i>BRG1</i>-mutant cell lines. In <i>BRG1</i>-mutant lung cancer cell lines, <i>BRM</i>-targeting shRNA decreased growth compared with control shRNA. In xenograft mice bearing <i>BRG1</i>-mutant human lung cancer cells, shRNA depletion of <i>BRM</i> decreased tumor growth compared with no depletion. Next steps could include developing and testing specific inhibitors of BRM (<i>see Depending on SWI/SNF, page 6</i>).</p> <p>SciBX 7(9); doi:10.1038/scibx.2014.251 Published online March 6, 2014</p>	Patent and licensing status unavailable	<p>Hoffman, G.R. <i>et al. Proc. Natl. Acad. Sci. USA</i>; published online Feb. 11, 2014; doi:10.1073/pnas.1316793111 Contact: Zainab Jagani, Novartis Institutes for BioMedical Research, Cambridge, Mass. e-mail: zainab.jagani@novartis.com Contact: Frank Stegmeier, same affiliation as above e-mail: frank.stegmeier@novartis.com</p>
Melanoma	Liver X receptor- β (NR1H2; LXR- β)	<p>Cell culture and mouse studies suggest agonizing LXR-β could be useful for treating metastatic melanoma. The liver X receptor can exist as two isoforms, LXR-α (NR1H3) or LXR-β. In cell culture, LXR agonists suppressed melanoma invasion and growth in cells with intact LXR-β but not in cells with LXR-β-targeting shRNA. In mouse models of melanoma, LXR agonists decreased tumor vascularization and metastasis and increased survival compared with vehicle. Next steps include preclinical testing of an optimized LXR-β-selective agonist.</p> <p>Rgenix Inc. has RGF-104, an LXR-β agonist derived from the tool compounds used in this study, in preclinical development for melanoma.</p> <p>Vitae Pharmaceuticals Inc. has two LXR-β agonists in preclinical development for atherosclerosis, acute coronary syndrome (ACS) and atopic dermatitis (<i>see Liver X receptor marks the spot, page 1</i>).</p> <p>SciBX 7(9); doi:10.1038/scibx.2014.252 Published online March 6, 2014</p>	Patent pending; licensed to Rgenix	<p>Pencheva, N. <i>et al. Cell</i>; published online Feb. 27, 2014; doi:10.1016/j.cell.2014.01.038 Contact: Sohail F. Tavazoie, The Rockefeller University, New York, N.Y. e-mail: stavazoie@mail.rockefeller.edu</p>

This week in therapeutics (continued)

Indication	Target/marker/pathway	Summary	Licensing status	Publication and contact information
Non-small cell lung cancer (NSCLC)	MEK; epidermal growth factor receptor (EGFR)	<p>Cell culture studies suggest antagonizing MEK or EGFR could be useful for treating <i>BRAF</i> mutation-positive NSCLC. About 6%–8% of NSCLC tumors have activating mutations in <i>BRAF</i>. In cultured NSCLC cells and human tissue samples with activating <i>BRAF</i> mutations, acquired resistance to <i>BRAF</i> inhibitors was associated with elevated MEK activation or constitutive EGFR signaling. In cell culture, small molecule MEK or EGFR inhibitors decreased treatment-acquired <i>BRAF</i> inhibitor resistance compared with vehicle controls. Next steps could include testing combinations of MEK or EGFR inhibitors with <i>BRAF</i> inhibitors in animal models of NSCLC. Tafinlar dabrafenib from GlaxoSmithKline plc and Zelboraf vemurafenib from Roche and Daiichi Sankyo Co. Ltd. are <i>BRAF</i> inhibitors marketed to treat <i>BRAF</i>-mutant melanoma. Tafinlar is also in Phase II testing for NSCLC. GSK also markets Mekinist trametinib, a small molecule MEK inhibitor, to treat <i>BRAF</i>-mutant melanoma. At least 12 companies have MEK inhibitors in Phase III or earlier testing to treat various cancers. More than a dozen EGFR inhibitors are marketed or in late-stage clinical development for a range of cancers.</p> <p>SciBX 7(9); doi:10.1038/scibx.2014.253 Published online March 6, 2014</p>	Patent and licensing status undisclosed	<p>Lin, L. <i>et al. Proc. Natl. Acad. Sci. USA</i>; published online Feb. 3, 2014; doi:10.1073/pnas.1320956111 Contact: Trever G. Bivona, University of California, San Francisco, Calif. e-mail: trever.bivona@ucsf.edu</p>
Pancreatic cancer	HER2 (EGFR2; ErbB2; neu); CD3; T cell receptor (TCR)	<p>Mouse and <i>in vitro</i> studies suggest bispecific antibodies targeting HER2 and either CD3 or the Vγ9 TCR could help eliminate pancreatic cancer cells. In cocultures of human pancreatic cancer cell lines with human $\gamma\delta$ T cells activated by synthetic phosphoantigen, addition of bispecific antibodies targeting HER2 and either CD3 or Vγ9 TCR increased the cytotoxic effect of $\gamma\delta$T cells on cancer cells compared with no treatment. In a mouse xenograft model of pancreatic cancer, the antibody targeting HER2 and Vγ9 TCR enhanced the antitumor cytotoxicity of adoptively transferred $\gamma\delta$ T cells. Next steps could include testing the bispecific antibody in additional mouse models of pancreatic cancer in comparison with individual HER2- and CD3- or Vγ9 TCR-specific antibodies.</p> <p>SciBX 7(9); doi:10.1038/scibx.2014.254 Published online March 6, 2014</p>	Patent and licensing status unavailable	<p>Oberg, H.-H. <i>et al. Cancer Res.</i>; published online Jan. 21, 2014; doi:10.1158/0008-5472.CAN-13-0675 Contact: Daniela Wesch, Kiel University, Kiel, Germany e-mail: wesch@immunologie.uni-kiel.de</p>
Thyroid cancer	Anaplastic lymphoma kinase (ALK); striatin calmodulin binding protein (STRN)	<p><i>In vitro</i> and mouse studies identified <i>STRN-ALK</i> fusions in highly aggressive thyroid cancers that could help assess prognosis and guide treatment. <i>STRN-ALK</i> fusions were identified in 3 of 256 well-differentiated papillary thyroid cancer samples, 3 of 35 poorly differentiated thyroid cancer samples and 1 of 24 anaplastic thyroid cancer samples. In mice, expression of <i>STRN-ALK</i> increased thyroid cell proliferation and subcutaneous tumor formation compared with expression of a kinase-dead fusion protein and led to constitutive ALK activity. The effects of the active transfects were blocked by the ALK inhibitor Xalkori crizotinib. Next steps could include validating the <i>STRN-ALK</i> fusion protein in additional cancer samples. Pfizer Inc. markets Xalkori to treat non-small cell lung cancer (NSCLC). At least eight other companies have ALK inhibitors in Phase II or earlier testing to treat cancer.</p> <p>SciBX 7(9); doi:10.1038/scibx.2014.255 Published online March 6, 2014</p>	Patent and licensing status unavailable	<p>Kelly, L.M. <i>et al. Proc. Natl. Acad. Sci. USA</i>; published online Feb. 3, 2014; doi:10.1073/pnas.1321937111 Contact: Yuri E. Nikiforov, University of Pittsburgh School of Medicine, Pittsburgh, Pa. e-mail: nikiforovyev@upmc.edu</p>

This week in therapeutics (continued)

Indication	Target/marker/ pathway	Summary	Licensing status	Publication and contact information
Cardiovascular disease				
Myocardial infarction (MI)	Cyclin A2 (CCNA2)	Pig studies suggest <i>CCNA2</i> gene therapy could help regenerate cardiac tissue and prevent fibrosis following MI. In pig models of MI, injection of an adenoviral vector encoding murine <i>Ccna2</i> into cardiac tissue near the infarct site increased ejection fraction—a measure of cardiac function—compared with pretreatment baselines and decreased fibrosis compared with empty vector. In the models, the gene therapy increased the number of actively dividing cardiomyocytes compared with empty vector. Planned work by VentriNova Inc. includes IND-enabling studies of an adenoviral vector encoding human CCNA2 in pig models of MI (<i>see Heart cells: no longer undivided, page 4</i>).	Patented by Columbia University; licensed to VentriNova	Shapiro, S.D. <i>et al. Sci. Transl. Med.</i> ; published online Feb. 19, 2014; doi:10.1126/scitranslmed.3007668 Contact: Hina W. Chaudhry, Icahn School of Medicine at Mount Sinai, New York, N.Y. e-mail: hina.chaudhry@mssm.edu
SciBX 7(9); doi:10.1038/scibx.2014.256 Published online March 6, 2014				
Myocardial infarction (MI)	Prostaglandin E ₂ receptor EP2 subtype (prostanoid EP2 receptor; PTGER2)	Mouse studies suggest activating PTGER2 with prostaglandin E ₂ (PGE ₂) could help replenish cardiomyocytes following MI. In a mouse model of MI, cardiomyocytes naturally repopulated the infarct border zone and a remote region up to 10 days post-MI. The process could be blocked with a cyclooxygenase (COX) inhibitor or COX-2-specific inhibitor up to five days post-MI. In the mouse model, the COX-2 downstream effector PGE ₂ increased stem cell-mediated cardiomyocyte repopulation compared with vehicle. In an aged mouse model of MI, injection of PGE ₂ increased stem cell-mediated cardiomyocyte repopulation at the infarct border zone compared with no treatment. Next steps include optimizing the delivery method for PGE ₂ .	Patent application filed; available for licensing	Hsueh, Y.-C. <i>et al. EMBO Mol. Med.</i> ; published online Jan. 21, 2014; doi:10.1002/emmm.201303687 Contact: Patrick C.H. Hsieh, National Cheng Kung University, Tainan, Taiwan e-mail: phsieh@mail.ncku.edu.tw
SciBX 7(9); doi:10.1038/scibx.2014.257 Published online March 6, 2014				
Myocardial infarction (MI)	Tissue inhibitor of metalloproteinases 3 (TIMP3)	Pig studies suggest recombinant TIMP3-containing, biodegradable hydrogels could help reduce damage following MI. After MI, matrix metalloproteinases are released and contribute to adverse remodeling. In a pig model of MI, injection of recombinant TIMP3-containing, biodegradable hydrogels into the left ventricle decreased left ventricle inflammatory markers, regional infarct expansion and left ventricular dilation and ejection fraction—a measure of cardiac function—compared with injection of either hydrogels without recombinant TIMP3 or saline. Next steps could include studies carried out over longer observational periods and dose-titration studies of recombinant TIMP3 in the hydrogel (<i>see Taking TIMP3 to heart, page 8</i>).	Patent application filed; unavailable for licensing	Eckhouse, S.R. <i>et al. Sci. Transl. Med.</i> ; published online Feb. 12, 2014; doi:10.1126/scitranslmed.3007244 Contact: Francis G. Spinale, University of South Carolina School of Medicine, Charleston, S.C. e-mail: cvctrc@uscmcd.sc.edu
SciBX 7(9); doi:10.1038/scibx.2014.258 Published online March 6, 2014				

This week in therapeutics (continued)

Indication	Target/marker/ pathway	Summary	Licensing status	Publication and contact information
Endocrine/metabolic disease				
Diabetes	Insulin	<p>Mouse studies suggest antibodies that prevent the recognition of specific autoimmunogenic insulin complexes could help treat type 1 diabetes. mAbs were produced that recognized a proinsulin peptide in complex with major histocompatibility complex class II (MHCII) protein when bound in register 3 but not in other registers. In a nonobese diabetic (NOD) mouse model for type 1 diabetes, injection of the mAb delayed the onset of type 1 diabetes and preserved pancreatic islet integrity, and it decreased the number of islet-infiltrating CD4⁺ and CD8⁺ T cells and B cells compared with injection of isotype-matched antibody controls. Ongoing work includes modifying the antibody for binding to human insulin and major histocompatibility complex class II DQ8 (HLA-DQ8) risk variant complexes.</p> <p>SciBX 7(9); doi:10.1038/scibx.2014.259 Published online March 6, 2014</p>	Patent filed covering the antibody and the peptide-based generation of the antibodies to protect against type 1 diabetes; available for licensing	<p>Zhang, L. <i>et al. Proc. Natl. Acad. Sci. USA</i>; published online Feb. 3, 2014; doi:10.1073/pnas.1323436111</p> <p>Contact: John W. Kappler, National Jewish Health, Denver, Colo. e-mail: kapplerj@njhealth.org</p>
Diabetes; obesity	Steroid sulfatase (STS)	<p>Mouse studies suggest hepatic STS overexpression could help treat obesity and diabetes. In genetic- or high-fat diet-induced female mouse models of type 2 diabetes, liver-specific STS overexpression decreased body weight, hepatic steatosis and inflammation and increased insulin sensitivity and estrogen activity compared with wild-type expression. Ovariectomy prevented the metabolic benefits of liver-specific STS overexpression. In a male mouse model of diet-induced obesity, hepatic STS overexpression decreased fat mass, hepatic steatosis and inflammation and increased lean mass and glucose tolerance compared with wild-type expression. Castration did not prevent the metabolic benefits of hepatic STS overexpression. Next steps could include identifying a therapeutic that induces STS expression in the liver.</p> <p>SciBX 7(9); doi:10.1038/scibx.2014.260 Published online March 6, 2014</p>	Unpatented; licensing status not applicable	<p>Jiang, M. <i>et al. J. Biol. Chem.</i>; published online Feb. 4, 2014; doi:10.1074/jbc.M113.535914</p> <p>Contact: Wen Xie, University of Pittsburgh, Pittsburgh, Pa. e-mail: wex6@pitt.edu</p>
Infectious disease				
HIV/AIDS	HIV gp120	<p><i>In vitro</i> studies suggest gp120 immunogens from patients that produce broadly neutralizing HIV antibodies could help develop prophylactic vaccines. Four gp120 immunogens based on peptide sequences from the patients' circulating HIV isolates bound to a variety of known broadly neutralizing HIV antibodies. Against a panel of diverse HIV isolates, serum from rabbits vaccinated with two of the four immunogens plus an adjuvant had broad but weak neutralizing activity. Next steps could include testing the vaccine strategy in animal models and improving potency.</p> <p>SciBX 7(9); doi:10.1038/scibx.2014.261 Published online March 6, 2014</p>	Patent and licensing status unavailable	<p>Carbonetti, S. <i>et al. PLoS One</i>; published online Jan. 23, 2014; doi:10.1371/journal.pone.0086905</p> <p>Contact: D. Noah Sather, Seattle BioMed, Seattle, Wash. e-mail: noah.sather@seattlebiomed.org</p>
HIV/AIDS	Not applicable	<p>Mouse studies suggest adenoviral vectors (AAVs) encoding broadly neutralizing HIV antibodies could protect against HIV vaginal transmission. In humanized mice, intramuscular injection of AAVs encoding various HIV antibodies prevented CD4⁺ T cell loss from mucosal tissues during vaginal challenge with clinically relevant HIV strains and decreased the number of animals with detectable viral load after repeated challenge compared with injection of luciferase-encoding vectors. Ongoing studies include clinical validation of the approach.</p> <p>SciBX 7(9); doi:10.1038/scibx.2014.262 Published online March 6, 2014</p>	Patent application filed; available for licensing	<p>Balazs, A.B. <i>et al. Nat. Med.</i>; published online Feb. 9, 2014; doi:10.1038/nm.3471</p> <p>Contact: David Baltimore, California Institute of Technology, Pasadena, Calif. e-mail: baltimo@caltech.edu</p>

This week in therapeutics (continued)

Indication	Target/marker/ pathway	Summary	Licensing status	Publication and contact information
Inflammation				
Allergy	Not applicable	<p>Mouse studies suggest peptide immunotherapy may be most effective for allergic diseases driven by effector memory T cells, such as seasonal allergies. In a mouse model of allergic airway inflammation induced by adoptive transfer of ovalbumin-experienced effector memory T cells, peptide immunotherapy prior to challenge blocked cytokine production and T cell function. When allergic airway inflammation was induced by adoptive transfer of central memory T cells, the T cells retained cytokine production upon antigen challenge after peptide immunotherapy. Next steps could include testing the peptide immunotherapy in allergic diseases specifically driven by effector memory T cells.</p> <p>SciBX 7(9); doi:10.1038/scibx.2014.263 Published online March 6, 2014</p>	Patent and licensing status unavailable	<p>Mackenzie, K.J. <i>et al. Proc. Natl. Acad. Sci. USA</i>; published online Feb. 10, 2014; doi:10.1073/pnas.1316178111 Contact: Stephen M. Anderton, The University of Edinburgh, Edinburgh, U.K. e-mail: steve.anderton@ed.ac.uk</p>
Neurology				
Cognitive dysfunction; Alzheimer's disease (AD)	Heat shock protein 90 (Hsp90)	<p>Mouse and <i>in vitro</i> studies suggest inhibiting Hsp90 could enhance cognitive function. In cultured primary rat neurons, an Hsp90 inhibitor increased heat shock transcription factor 1 (HSF1)-dependent expression of pre- and postsynaptic proteins compared with vehicle control, leading to elevated synaptic transmission and protection against spine loss after treatment with β-amyloid (Aβ). In mice, intracerebroventricular injection of Aβ plus the inhibitor rescued synaptic protein expression and decreased memory loss in a fear conditioning test compared with injection of Aβ alone. Ongoing work includes testing an undisclosed proprietary brain-permeable Hsp90 inhibitor in a mouse model of AD.</p> <p>SciBX 7(9); doi:10.1038/scibx.2014.264 Published online March 6, 2014</p>	Unpatented; unlicensed	<p>Chen, Y. <i>et al. J. Neurosci.</i>; published online Feb. 12, 2014; doi:10.1523/JNEUROSCI.0151-13.2014 Contact: Francesca-Fang Liao, The University of Tennessee Health Science Center College of Medicine, Memphis, Tenn. e-mail: fliao@uthsc.edu</p>
Spinal cord injury (SCI)	Neurotrophic tyrosine kinase receptor 2 (NTRK2; TrkB); NTRK3 (TrkC); chondroitin sulfate proteoglycan (CSPG)	<p>Studies in rats suggest engineered Schwann cells could be useful for treating SCI. Schwann cells were engineered to coexpress a bifunctional neurotrophin that activates TrkB and TrkC and a bacterial chondroitinase that degrades the extracellular matrix component CSPG. In a rat model of SCI, transplanted Schwann cells expressing the neurotrophin and chondroitinase decreased inflammation and increased axonal regeneration and motor function compared with cells expressing either protein alone. Next steps could include developing methods for autologous transplantation of patient-derived Schwann cells.</p> <p>Acorda Therapeutics Inc. has chondroitinase in preclinical development for SCI.</p> <p>SciBX 7(9); doi:10.1038/scibx.2014.265 Published online March 6, 2014</p>	Patent and licensing status undisclosed	<p>Kanno, H. <i>et al. J. Neurosci.</i>; published online Jan. 29, 2014; doi:10.1523/JNEUROSCI.2661-13.2014 Contact: Mary B. Bunge, University of Miami, Miami, Fla. e-mail: mbunge@miami.edu</p>

This week in therapeutics (continued)

Indication	Target/marker/ pathway	Summary	Licensing status	Publication and contact information
Pulmonary disease				
Pulmonary fibrosis	Protein kinase A (PKA)	<p><i>In vitro</i> and mouse studies suggest noscapine could help treat pulmonary fibrosis. In human lung fibroblasts, noscapine inhibited transforming growth factor-β (TGFB; TGFβ)-induced myofibroblast differentiation and activated antifibrotic PKA, whereas adenoviral-mediated expression of a PKA inhibitor prevented the effects on differentiation. In a mouse model of chemically induced pulmonary fibrosis, noscapine decreased fibrosis compared with vehicle control. Noscapine is a generic benzyloquinoline alkaloid available over the counter in some countries in anticough products. In 2009, KineMed Inc. filed a patent covering the use of the compound to treat pulmonary fibrosis; its development status is unavailable.</p> <p><i>SciBX</i> 7(9); doi:10.1038/scibx.2014.266 Published online March 6, 2014</p>	Patent and licensing status unavailable	<p>Kach, J. <i>et al. J. Biol. Chem.</i>; published online Feb. 3, 2014; doi:10.1074/jbc.M113.546812 Contact: Nickolai O. Dulin, The University of Chicago, Chicago, Ill. e-mail: ndulin@medicine.bsd.uchicago.edu</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			
Automated, massively parallel RNA single-cell sequencing framework (MARS-Seq) for analyzing transcriptional states in thousands of single cells	<i>In vitro</i> studies suggest MARS-Seq can be applied to understand tissue heterogeneity in disease. Fluorescence-activated cell sorting was used to pool homogenous cell populations. RNA sequencing on the pooled samples yielded transcriptional profiles for 200–1,500 RNA molecules per cell, and unsupervised clustering distinguished heterogeneous transcriptional profiles. In a proof-of-concept application, the method distinguished between B cells, NK cells, macrophages, monocytes, plasmacytoid dendritic cells and other subtypes of dendritic cells derived from 4,000 mouse spleen cells. Next steps include improving RNA extraction efficiency and increasing multiplexing capacity from 1,600 to 10,000 cells per sequencing lane. SciBX 7(9); doi:10.1038/scibx.2014.267 Published online March 6, 2014	Patent filed; available for licensing from the Weizmann Institute of Science through Yeda Research and Development Company Ltd.	Jaitin, D.A. <i>et al. Science</i> ; published online Feb. 14, 2014; doi:10.1126/science.1247651 Contact: Ido Amit, Weizmann Institute of Science, Rehovot, Israel e-mail: ido.amit@weizmann.ac.il Contact: Amos Tanay, same affiliation as above e-mail: amos.tanay@weizmann.ac.il
Disease models			
Clustered, regularly interspaced short palindromic repeats (CRISPR) genome editing to produce genetically modified monkeys	Primate studies suggest CRISPR could be used to develop genetically modified monkeys that model disease. In single-cell cynomolgus monkey embryos, injection of a pool of five single guide RNAs (sgRNAs) targeting peroxisome proliferation-activated receptor- γ (PPARG; PPAR γ), recombinant activating gene 1 (RAG1) and nuclear receptor subfamily 0 group B member 1 (NR0B1) plus CRISPR-associated 9 (Cas9) mRNA resulted in embryos with simultaneous disruptions in two target genes. In infant monkeys born after embryos were transferred to female monkeys, umbilical cord, placenta and ear puncture tissues from twin monkeys had the same genetic modifications in <i>Pparγ</i> and <i>Rag1</i> . Next steps include developing germline-modified monkeys using the strategy. SciBX 7(9); doi:10.1038/scibx.2014.268 Published online March 6, 2014	Findings unpatented; unavailable for licensing	Niu, Y. <i>et al. Cell</i> ; published online Jan. 30, 2014; doi:10.1016/j.cell.2014.01.027 Contact: Jiahao Sha, Nanjing Medical University, Nanjing, China e-mail: shajh@njmu.edu.cn Contact: Xingxu Huang, Model Animal Research Center of Nanjing University, Nanjing, China e-mail: xingxuhuang@mail.nju.edu.cn Contact: Weizhi Ji, Yunnan Key Laboratory of Primate Biomedical Research, Kunming, China e-mail: wji@kbimed.com
Humanized bone marrow, liver and thymus (huBLT) mouse model of Kaposi's sarcoma-associated herpes virus (KSHV) infection	The huBLT mouse model could be used to study pathogenesis and transmission of KSHV. The model was previously generated using nonobese diabetic (NOD) severe combined immunodeficiency (SCID) mice that lacked IL-2 receptor γ -chain (Cd132) and showed susceptibility to viruses that infect humans. In the huBLT mouse, oral or intravaginal inoculation of KSHV established latent and lytic infection in human B cells and macrophages in the spleen and latent infection in human macrophages in the skin. Next steps include using the model to determine the transmission route after KSHV exposure and how it can lead to persistent infection. SciBX 7(9); doi:10.1038/scibx.2014.269 Published online March 6, 2014	Unpatented; licensing status not applicable	Wang, L.-X. <i>et al. Proc. Natl. Acad. Sci. USA</i> ; published online Feb. 10, 2014; doi:10.1073/pnas.1318175111 Contact: Charles Wood University of Nebraska, Lincoln, Neb. e-mail: cwood1@unl.edu Contact: Qingsheng Li, same affiliation as above e-mail: qli4@unl.edu

This week in techniques (continued)

Approach	Summary	Licensing status	Publication and contact information
Drug platforms			
Induced pluripotent stem (iPS) cell-derived immortalized megakaryocyte progenitor cell lines as a self-renewing source for human platelets	<i>In vitro</i> and mouse studies suggest iPS cell-derived platelets could be used for clinical applications. Stable, immortalized megakaryocyte progenitor cell lines were generated from iPS cells by overexpression of BMI1 polycomb ring finger oncogene (BMI1), Bcl-x _i and c-Myc (MYC), and the cells produced platelets when transgene expression was turned off. <i>In vitro</i> , aggregation of immortalized megakaryocyte progenitor cell line-derived platelets was lower than that of fresh human platelets but comparable to that of other iPS cell-derived platelets or pooled human endogenous platelets. In a mouse model of thrombocytopenia, the platelets adhered to laser-exposed vessel walls and contributed to thrombus formation. Next steps could include optimizing megakaryocyte maturation, efficiency of platelet release into liquid culture systems and platelet yield per megakaryocyte.	Patent application filed; in negotiations for licensing to an undisclosed company; unavailable for licensing	Nakamura, S. <i>et al. Cell Stem Cell</i> ; published online Feb. 13, 2014; doi:10.1016/j.stem.2014.01.011 Contact: Koji Eto, Kyoto University, Kyoto, Japan e-mail: kojieto@cira.kyoto-u.ac.jp
	SciBX 7(9); doi:10.1038/scibx.2014.270 Published online March 6, 2014		
Knockdown of endogenous proteins by peptide-directed lysosomal degradation	Rat studies suggest a chaperone-mediated autophagy-targeting motif (CTM) that directs proteins toward lysosomal degradation could provide a method for knockdown of endogenous proteins. Previous cell-based studies showed that CTM-containing fusion proteins are degraded by the lysosome through chaperone-mediated autophagy. In cultured rat cortical neurons, a CTM-tagged, death-associated protein kinase 1 (DAPK1; DAPK)-targeting peptide decreased levels of DAPK1 and oxidative stress-induced damage compared with a CTM-deficient control peptide. In a rat model of focal ischemia, the CTM-tagged, DAPK1-targeting peptide decreased levels of DAPK1 in ischemic brain tissue and ischemic damage compared with the CTM-deficient control peptide. Next steps include developing targeting peptides for disease-causing proteins related to Parkinson's disease (PD), Alzheimer's disease (AD) and cancer.	Patent application filed by The University of British Columbia; available for licensing	Fan, X. <i>et al. Nat. Neurosci.</i> ; published online Jan. 26, 2014; doi:10.1038/nn.3637 Contact: Yu Tian Wang, The University of British Columbia, Vancouver, British Columbia, Canada e-mail: ytwang@brain.ubc.ca
	SciBX 7(9); doi:10.1038/scibx.2014.271 Published online March 6, 2014		
Small molecules plus transient expression of transcription factors to convert fibroblasts to pancreatic β cells	Fibroblasts transiently expressing transcription factors and treated with small molecules could provide transplantable pancreatic β cells to help treat type 1 diabetes. In mouse fibroblast cultures, transient expression of four pluripotency transcription factors plus delivery of specific small molecule combinations produced transdifferentiated endoderm-like cells that could be further converted into pancreatic progenitor-like cells and all three pancreatic lineages. In a mouse model of hyperglycemia, transplanted pancreatic progenitor-like cells gave rise to all three pancreatic cell types, including glucose-responsive, insulin-producing β cells, which reduced hyperglycemia. Next steps include translating the approach to human cells and trying to substitute the genetic introduction of pluripotency factors for noninvasive methods.	Patent application filed; available for licensing	Li, K. <i>et al. Cell Stem Cell</i> ; published online Feb. 6, 2014; doi:10.1016/j.stem.2014.01.006 Contact: Sheng Ding, University of California, San Francisco, Calif. e-mail: sheng.ding@gladstone.ucsf.edu
	SciBX 7(9); doi:10.1038/scibx.2014.272 Published online March 6, 2014		
Imaging			
Micrococcal nuclease-activated fluorescent oligonucleotide probes to image <i>Staphylococcus aureus</i> infection	<i>In vitro</i> and mouse studies suggest a nuclease-activated fluorescent oligonucleotide probe could noninvasively image and diagnose <i>S. aureus</i> infections. The oligonucleotide probe was specifically cleaved by <i>S. aureus</i> micrococcal nuclease and was resistant to degradation by serum nucleases. In mice with thigh muscle infection by wild-type <i>S. aureus</i> , intravenously injected probes were activated and caused fluorescence at the infection site, whereas probe activation was decreased or absent in uninfected muscles or muscles infected with a micrococcal nuclease-deficient strain. Next steps include exchanging the fluorophore on the probe with a fluorophore suitable for clinical imaging.	Patent application filed; available for licensing	Hernandez, F. <i>et al. Nat. Med.</i> ; published online Feb. 2, 2014; doi:10.1038/nm.3460 Contact: James O. McNamara II, The University of Iowa, Iowa City, Iowa e-mail: james-mcnamara@uiowa.edu
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