

## THIS WEEK

## ANALYSIS

## COVER STORY

**1 Targeting fibrotic integrin**

An international team of researchers has shown that the myofibroblast-expressed integrin  $\alpha_v$  subunit drives fibrosis and that a small molecule integrin  $\alpha_v$  antagonist from Antegrin Therapeutics can attenuate the process in mice. The biotech is developing an improved version of the compound for pulmonary fibrosis.

## TRANSLATIONAL NOTES

**4 A conversation with Chris Lipinski**

Although the 'rule of five' has altered medicinal chemistry for oral small molecule drugs, Chris Lipinski believes that predicting the behavior of newer biologics might not be far off, and optimization of RNA or protein delivery could be the opportunity for the next big breakthrough in computer-based predictions.

## TARGETS &amp; MECHANISMS

**7 A gut feeling about butyrate**

Inflammatory conditions of the gut have long been associated with imbalances in mucosal levels of microflora-produced short-chain fatty acids, but the underlying mechanisms were unknown. Two separate groups in the U.S. and Japan have reported how one such bacterial fatty acid can promote mucosal health.

## THE DISTILLERY

**10 This week in therapeutics**

Mimicking miR-141 and miR-219 to prevent bone metastasis; inhibiting ATGL to alleviate metabolic disorders; antagonizing TWEAK to promote muscle regeneration; and more...

**17 This week in techniques**

An *in vitro* screen to detect genetic signatures associated with sensitivity to targeted cancer therapeutics; a mouse model of intrahepatic cholangiocarcinoma; an immunosuppression regimen to prevent immunotoxin neutralization; and more...

## INDEXES

**20 Company and institution index****20 Target and compound index**

# Targeting fibrotic integrin

By Benjamin Boettner, Associate Editor

Fibrosis has long been associated with the activation of transforming growth factor- $\beta$  by integrin, but the mechanism underlying the process *in vivo* was not known. Now, an international team has shown that the myofibroblast-expressed integrin  $\alpha_v$  subunit drives fibrogenesis and has proof of concept for therapeutic intervention with a small molecule integrin  $\alpha_v$  antagonist from Antegrin Therapeutics LLC.<sup>1</sup>

The biotech is developing an improved version of the lead compound for idiopathic pulmonary fibrosis (IPF).

Fibrosis is a tissue repair process triggered by injury or chronic inflammation that results in excessive accumulation of connective tissue, which over time can lead to permanent scarring and organ failure. Fibrosis occurs in end-stage liver disease, IPF and kidney disease.<sup>2</sup>

In the liver, myofibroblasts produce integrin  $\alpha_v$  (CD51)-containing complexes on their surface that activate latent transforming growth factor- $\beta$  (TGFB; TGF $\beta$ ) reservoirs in the extracellular matrix of different cell types. TGFB in turn induces myofibroblasts to produce collagen and other extracellular matrix proteins that constitute the fibrotic tissue.

At the molecular level, *in vitro* and *in vivo* studies have shown that TGFB activation results from integrin  $\alpha_v$  subunit-containing complexes interacting with an arginine-glycine-aspartic acid (RGD) motif on TGF $\beta$ . Whether this mechanism also occurs in myofibroblasts and actually drives fibrosis *in vivo* had yet to be determined. A key impediment was the lack of a genetic system for manipulating myofibroblasts *in vivo*.

An international team led by Dean Sheppard, a professor in the Department of Medicine and director of the Lung Biology Center at the University of California, San Francisco, has now devised a strategy to genetically manipulate liver-specific myofibroblasts in mice.

The researchers controlled gene activation in myofibroblasts by generating mice with conditional knockout of pericytes, a class of cells that envelop and protect capillaries and venules in a variety of tissues

**“The fibrosis models explored thus far are chemical- or injury-induced models of fibrosis. It will be important to see if the compound works in chronic disease settings and in models of fibrosis where chronic infection like HCV is a major driver of fibrosis.”**

— Thomas Wynn,  
National Institute of Allergy and  
Infectious Diseases

**EDITORIAL****Editor-in-Chief:** Karen Bernstein, Ph.D.**Managing Editor:** Gaspar Taroncher-Oldenburg, Ph.D.**Executive Editor:** Steve Edelson**Senior Editors:** Tracey Baas, Ph.D.; Amy Donner, Ph.D.; C. Simone Fishburn, Ph.D.**Associate Editor:** Benjamin Boettner, Ph.D.**Writers:** Chris Cain, Ph.D.; Michael J. Haas; Kai-Jye Lou; Lauren Martz; Lev Osherovich, Ph.D.**Research Director:** Walter Yang**Research Manager:** Kevin Lehnbeuter**Production Editors:** Brandy Cafarella; Carol Evangelista; Ivelisse Robles**Copy Editor:** Nicole DeGennaro**Editorial Assistant:** Mark Zipkin**Design:** Claudia Bentley; Miles DaviesFor inquiries, contact [editorial@scibx.com](mailto:editorial@scibx.com)**PUBLISHING****Publisher:** Peter Collins, Ph.D.**Associate Publishers:** Gaspar Taroncher-Oldenburg, Ph.D.; Eric Pierce**Marketing:** Sara Girard; Greg Monteforte**Technology:** Anthony Barrera; Julia Kulikova**Sales:** Ron Rabinowitz; Dean Sanderson; Tim Tulloch**OFFICES****BioCentury Publications, Inc.**San Francisco  
PO Box 1246  
San Carlos, CA 94070-1246  
T: +1 650 595 5333Chicago  
20 N. Wacker Drive, Suite 1465  
Chicago, IL 60606-2902  
T: +1 312 755 0798United Kingdom  
T: +44 (0)18 6551 2184Washington, DC  
2008 Q Street, NW, Suite 100  
Washington, DC 20009  
T: +1 202 462 9582**Nature Publishing Group**New York  
75 Varick Street, 9th Floor  
New York, NY 10013-1917  
T: +1 212 726 9200London  
The Macmillan Building  
4 Crinan Street  
London N1 9XW  
United Kingdom  
T: +44 (0)20 7833 4000Tokyo  
Chiyoda Building 6F  
2-37 Ichigayatamachi  
Shinjuku-ku, Tokyo 162-0843  
Japan  
T: +81 3 3267 8751

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

Copyright © 2013 Nature Publishing Group ALL RIGHTS RESERVED.

No part of the SciBX publication or website may be copied, reproduced, retransmitted, disseminated, sold, distributed, published, broadcast, circulated, commercially exploited or used to create derivative works without the written consent of the Publishers. Information provided by the SciBX publication and website is gathered from sources that the Publishers believe are reliable; however, the Publishers do not guarantee the accuracy, completeness, or timeliness of the information, nor do the Publishers make any warranties of any kind regarding the information. The contents of the SciBX publication and website are not intended as investment, business, tax or legal advice, and the Publishers are not responsible for any investment, business, tax or legal opinions cited therein.

and organs.<sup>3</sup> The team targeted hepatic stellate cells (HSCs)—the liver-specific pericytes and direct precursors of myofibroblasts in liver—to specifically manipulate gene expression in myofibroblasts.

In mice lacking myofibroblast integrin  $\alpha_v$  expression, attempts to induce fibrosis led to low levels of fibrosis markers such as actin  $\alpha_2$  smooth aorta muscle (Acta2;  $\alpha$ -Sma) compared with levels seen in mice expressing the integrin  $\alpha_v$  subunit. The mice lacking integrin  $\alpha_v$  expression also developed minimal fibrosis.

In culture, HSCs from the mice lacking integrin  $\alpha_v$  expression also produced substantially less active TGF $\beta$ 1 and had decreased TGF $\beta$ 1 signaling compared with HSCs expressing the integrin  $\alpha_v$  subunit.

A similar mechanism was at work in the lung and kidney, in which myofibroblasts also drive fibrosis. Indeed, disrupting integrin  $\alpha_v$  in an equivalent cell population in these tissues protected mice from developing fibrosis.

Finally, the researchers provided evidence that targeting profibrotic integrin  $\alpha_v$  with a small molecule RGD peptidomimetic antagonist, CWHM 12, inhibited liver and pulmonary fibrosis progression in mice. CWHM 12 competes with the activating RGD motif in latent TGF $\beta$ 1 for integrin  $\alpha_v$  binding.

Results were published in *Nature Medicine*.

The team included researchers from **The University of Edinburgh, Saint Louis University, The University of Texas MD Anderson Cancer Center, Harvard Medical School, Uppsala University, the Karolinska Institute, the Max Planck Institute for Molecular Biomedicine and the University of Muenster.**

UCSF has filed for a patent covering the identification of integrin  $\alpha_v$  complexes.

“Integrin  $\alpha_v$  inhibition on myofibroblasts as the theme emerging from the study builds on a growing body around mechanisms underlying fibrosis, including pathways that are conserved between organs,” said Scott Friedman, dean for therapeutic discovery and a professor of medicine, liver diseases, pharmacology and systems therapeutics at the **Icahn School of Medicine at Mount Sinai**. “The treatment strategy is a nice example showing that antagonizing a conserved pathway could impact fibrosis in more than one organ. Integrin  $\alpha_v$  is eminently targetable and accessible to inhibitory compounds, including antibodies.”

Thomas Wynn, chief of the immunopathogenesis section of the NIH’s **National Institute of Allergy and Infectious Diseases**, agreed. “This is indeed a very exciting study as it suggests integrin  $\alpha_v$  inhibition in myofibroblasts may prove highly efficacious in a wide variety of fibrotic diseases,” he said.

**The myofibroblast advantage**

According to Sheppard, one of the major advantages of his team’s strategy is that targeting integrin-mediated TGF $\beta$ 1 activation has the potential advantage of decreasing toxicity compared with targeting all TGF $\beta$ 1.

“This could be an important opportunity, since no drug specifically tackling fibrosis in any organ is available,” he said.

Scott Turner, VP of R&D at biomarker discovery company **KineMed Inc.**, said that it will be important to determine the effect of inhibiting integrin  $\alpha_v$  in healthy tissues. “This will inform about safety liabilities. In addition, there could be a chance that the integrin might play a role in normal wound healing and scarring processes apart from fibrosis,” he said.

According to Friedman, broadly targeting TGF $\beta$ 1 directly could have adverse effects such as infection or neoplasia. “The appeal of the present study is that it circumvents this risk by rendering TGF $\beta$ 1 inhibition cell type and tissue specific, thus minimizing the risk,” he said.

Wynn said that it will be important to determine whether targeting the integrin  $\alpha_v$  subunit with a small molecule inhibitor will prove safe and effective in the long term “given that the TGF $\beta$ 1 pathway is potentially dangerous to disrupt over a long period of time. It also will be vital to find out if the small molecule inhibitor only works by blocking the TGF $\beta$ 1 pathway or if it also works by blocking other profibrotic mechanisms.”

Wynn also noted that TGF $\beta$ 1 is not the only mediator of fibrosis.

Sheppard told *SciBX* that his team is planning to determine how integrin-mediated TGF $\beta$ 1 activation contributes to different fibrotic processes. He also said that the team is focusing on identifying the integrin  $\beta$  subunits in complex with integrin  $\alpha_v$  that are relevant to fibrosis.

“The fibrosis models explored thus far are chemical- or injury-induced models of fibrosis,” noted Wynn. “It will be important to see if the compound works in chronic disease settings and in models of fibrosis where chronic infection like HCV is a major driver of fibrosis. Long-term toxicity studies will be needed before the drug is used in humans, and it will also be important to determine if it is efficacious in models other than mice.”

“Each fibrosis indication requires its own set of preclinical models. For small molecules like the one featured in the study, the therapeutic window is always a critical parameter to assess,” noted Shelia Violette, senior director of the tissue injury and fibrosis research unit at **Biogen Idec Inc.** “In addition, developing a biomarker strategy that can help read out blockade of the target in early clinical trials can be of great use. These readouts should provide proof of biology and a sense of specificity and saturation of the integrin  $\alpha_v$  target by the compound.”

Biogen’s STX-100, a mAb specific to integrin  $\alpha_v\beta_6$  complexes, is in Phase II testing to treat IPF.

### Enter Antegrin

Antegrin, a spinout of the **Center for World Health & Medicine at Saint Louis University**, is developing therapies for fibrotic diseases with an initial focus on IPF. The company provided the integrin  $\alpha_v$  inhibitor CWHM 12 for the published study. David Griggs and Peter Ruminski, cofounders and scientific advisers at the company, are coauthors of the paper.

Griggs is director of cellular and molecular biology at the Center for World Health & Medicine and an adjunct assistant professor of pharmacology and physiology at the **Saint Louis University School of Medicine**. Ruminski is the center’s executive director.

Saint Louis University has filed for patents covering composition of matter and use of integrin inhibitors. Antegrin has an option to obtain an exclusive license to the IP.

Griggs told *SciBX* that “although CWHM 12 has been an excellent tool compound for early studies, later unpublished compounds are superior in regard to aqueous solubility and potency to inhibit integrin  $\alpha_v$ . Antegrin is synthesizing and profiling additional integrin inhibitors from which to select the candidate(s) for further development.”

Ruminski added, “Antegrin’s next big milestone is the selection of a clinical development candidate for inhalation delivery, which we think will be attractive for treatment of idiopathic pulmonary fibrosis. Our compounds have physicochemical properties that make them favorable for pulmonary delivery.”

This delivery method can reach higher concentrations with less toxicity in the lung, according to the company.

Boettner, B. *SciBX* 6(46); doi:10.1038/scibx.2013.1308  
Published online Dec. 5, 2013

### REFERENCES

- Henderson, N.C. *et al. Nat. Med.*; published online Nov. 10, 2013; doi:10.1038/nm.3282  
**Contact:** Dean Sheppard, University of California, San Francisco, Calif.  
e-mail: [dean.sheppard@ucsf.edu](mailto:dean.sheppard@ucsf.edu)
- Contact:** Neil C. Henderson, The University of Edinburgh, Edinburgh, U.K.  
e-mail: [neil.henderson@ed.ac.uk](mailto:neil.henderson@ed.ac.uk)
- Wynn, T.A. & Ramalingam, T.R. *Nat. Med.* **18**, 1028–1040 (2012)
- Foo, S.S. *et al. Cell* **124**, 161–173 (2006)

### COMPANIES AND INSTITUTIONS MENTIONED

**Antegrin Therapeutics LLC**, St. Louis, Mo.  
**Biogen Idec Inc.** (NASDAQ:BIIB), Weston, Mass.  
**Center for World Health & Medicine at Saint Louis University**, St. Louis, Mo.  
**Harvard Medical School**, Boston, Mass.  
**Icahn School of Medicine at Mount Sinai**, New York, N.Y.  
**Karolinska Institute**, Stockholm, Sweden  
**KineMed Inc.**, Emeryville, Calif.  
**Max Planck Institute for Molecular Biomedicine**, Muenster, Germany  
**National Institute of Allergy and Infectious Diseases**, Bethesda, Md.  
**National Institutes of Health**, Bethesda, Md.  
**Saint Louis University**, St. Louis, Mo.  
**Saint Louis University School of Medicine**, St. Louis, Mo.  
**University of California, San Francisco**, Calif.  
**The University of Edinburgh**, Edinburgh, U.K.  
**University of Muenster**, Muenster, Germany  
**The University of Texas MD Anderson Cancer Center**, Houston, Texas  
**Uppsala University**, Uppsala, Sweden

# A conversation with Chris Lipinski

By C. Simone Fishburn, Senior Editor

Chris Lipinski, author of the 1997 ‘rule of five’,<sup>1</sup> believes that although the rule has altered medicinal chemistry for oral small molecule drugs, predicting the behavior of newer biologics might not be far off, and optimization of RNA or protein delivery could be the opportunity for the next big breakthrough in computer-based predictions.

The rule of five, developed while Lipinski was a senior research fellow at **Pfizer Inc.**, outlines four simple criteria to help design orally available drugs. *SciBX* talked with Lipinski, now scientific advisor at **Melior Discovery Inc.**, to hear his thoughts on the impact of the rule of five and how he thinks current predictive approaches might advance drug design.

*SciBX*: What was the impetus that led you to develop the rule of five?

*Chris Lipinski*: At that time, 1997, at least 90% of the small molecule medicinal chemistry efforts were directed at oral compounds. People were heavily influenced by a high throughput screening philosophy and were making large numbers of compounds that were evaluated for potency without regard for anything else.

Normally, increasing the potency means making compounds that are larger and more lipophilic, which generates a lot of problems for getting good oral absorption.

The original purpose of the rule of five was to shift the physicochemical property profiles of compounds being made by medicinal chemists to increase the likelihood of getting an orally active compound (see **Box 1**, “Rules of engagement”).

*SciBX*: Do you believe the rule of five has changed how medicinal chemists create compounds?

*CL*: Absolutely. Based on medicinal chemistry sessions at the **American Chemical Society** national meeting, where some of the hottest compounds going into the clinic are presented for the first time, it seems that on average more than 50% of the effort goes toward optimizing properties other than potency.

I would say that across the board, those simple principles were successful. At **Pfizer** they definitely moved the medicinal chemistry profiles in a positive direction, and at most other organizations I think they did also.

*SciBX*: When you came up with the rule of five were there compound classes you knew or suspected it would not apply to?

*CL*: Yes. At **Pfizer** we looked for compounds that were orally active and broke the rule and found they were mostly natural products.

One of the big problems with natural products is that we don’t understand shape—typically natural products are large and can form intramolecular hydrogen bonds. We do not do well computationally with cyclic structures like these and with predicting restrained conformational mobility.

For example, cyclosporine breaks every parameter in the rule of five, but in fact with some formulation work you get acceptable oral absorption because cyclosporine is a macrocyclic peptide that behaves like a molecular chameleon.

In a lipophilic environment, the *N*-methyl groups, which are greasy, stick on the outside and all the polar groups are buried on the inside, whereas when the molecule is in a polar aqueous environment it reverses so all the lipophilic *N*-methyl groups are on the inside and all the polar ones are on the outside.

I strongly suspect that many of the natural products that are orally active and have good membrane penetration properties in fact have this molecular chameleon-type property. We could try to come up with rules for that. But we don’t have any way of taking large lists of complex natural products and figuring out what the shape would be in a lipophilic or hydrophilic environment and whether the energy levels would support the compounds flipping shape.

## Box 1. Rules of engagement.

Chris Lipinski and colleagues at **Pfizer Inc.** defined the ‘rule of five’ after analyzing the physicochemical properties of over 2,000 drugs.<sup>1</sup> They proposed that compounds would be more likely to be orally available if they had: (1) molecular weight lower than 500 Da, (2) hydrophobicity measure  $\log P$  less than 5, (3) fewer than 5 hydrogen bond donors and (4) fewer than 10 hydrogen bond acceptors. All the numbers in the four listed criteria are multiples of five—hence the name ‘rule of five’.

The rule of five remains a topic of debate among medicinal chemists

who employ it broadly but continue to discuss its pros and cons.<sup>2</sup> *SciBX* addressed this in the conversation with Lipinski.

*SciBX*: What are the main limitations of using the rule of five in drug discovery?

*Chris Lipinski*: The problem with the rule of five and with other rules is that they can be misused. The rule of five is a rule with hard cutoffs:  $\log P$  greater than 5 is bad;  $\log P$  less than 5 is good. To say a compound with  $\log P$  of 4.99 is acceptable and with  $\log P$  [of] 5.01 isn’t makes

no sense whatsoever, so you need to use common sense.

If your strategy is to screen out anything with a  $\log P$  greater than 3 and a molecular weight greater than 400 you’ll discover many GPCR ligands, phosphodiesterase targets and some kinases, but you will miss just about every possible protein-protein interaction target and you’ll have a lot of trouble with peptidergic GPCRs and protease targets.

So by being too limiting on the rules you eliminate great swaths of target space that you’d really like to interrogate.

—CSF

If we understood that, then we could learn from evolution and come up with designs that might help us get into those difficult targets where the ligands are out of the rule of five space.

*SciBX:* Your original predictions related to small molecule drugs. Can we make similar predictions for other modalities?

*CL:* We are beginning to see better software for dealing with proteins. I often talk about the ‘in-between-world size’.

Three years ago, if you had something that was [molecular weight] 20 kDa, the small molecule software didn’t work well.

Now, we are getting to the position that we can experimentally make complex agents as single compounds that differ by post-translational modification or position of pegylation, even though they’re in the biologic size range.

That gets closer to the world of small molecules, which deals with discrete single compounds. Then the kinds of rules and discoveries about SAR properties and matched pairs in the small molecule world might also apply to the larger molecules.

I think the driver for progress here will be technology advancements for controlling the synthesis and manufacture of some of these complex compounds.

*SciBX:* Do you think there are newer strategies that could help improve on the rule of five?

*CL:* Matched fragment pairs add value, as they typically occur in lead optimization, and unlike the physicochemical properties used in the rule of five, this approach directly implements experimental data from *in vitro* and *in vivo* screening.

If you have a molecule that looks good and has one property such as clearance that is a problem, the team can make a series of matched fragment pairs and look at specific ADME parameters to help optimize the molecule.

*SciBX:* There are various software packages that predict how small molecules will behave based on their chemical structures. How good do you think those programs are, and what is the most effective way to implement the information they yield?

*CL:* In general, the usefulness depends on how structurally similar your new compound is to the software’s training set of molecules.

For absorption, with good experimental input parameters you can generate fairly good simulations of the plasma profile of the compound and some of the clearance parameters. That aspect is definitely useful.

For predictive software, like Derek Nexus, the main value is in the toxicity alerts. People would seldom exclude a compound at a post-screening stage because of a general alert in a toxicity-prediction program. But if they receive an alert for a specific organ toxicity that is based on testing data in the literature [such as Derek provides], they can

look at aspects of the chemistry that can be changed to resolve that issue but retain potency. The specific character of the toxicity prediction makes it easier to test whether the prediction of a problem is correct and whether the new chemistry changes have solved the problem.

*SciBX:* Has computational prediction peaked or can it still improve?

*CL:* It could get better from two angles.

First, the data quality; predictions are only as good as data quality. There are increasing numbers of people talking about this in the biology and chemistry realms. In chemistry, some journals require quality parameters to confirm the compound’s identity and its level of purity.

Second, there is a big movement toward cooperation and collaboration between the different players, for example, by precompetitive data sharing. This can increase the amount of data being used to make the predictions and so improve the quality.

For example, it makes sense for organizations to combine datasets on matched fragment pairs as the quantity of relevant experimental data that comes out of high throughput screening is very small. Pooling data will make it more likely you’ll get matched fragment pairs that enable you to deduce rules about which fragments are more metabolically stable or give you lower toxicity in specific assays.

*SciBX:* Do you believe that ultimately these predictive programs can lead to shorter drug development times and cost savings that will affect the industry?

*CL:* I’m not sure about shorter. It may reduce attrition. These kinds of tools used efficiently and knowledgeably can eliminate a lot of the mistakes and wasted effort that currently goes on.

*SciBX:* What has surprised you most in the field of molecule design and predicting drug behavior, and what are the biggest successes and failures?

*CL:* The success of fragment screening took me completely by surprise. If someone had told me 15 years ago that you could have a small lipophilic fragment that would bind selectively, and that screening compounds in the 100  $\mu\text{M}$  to [low] mM range could give you enough information to optimize and reach a clinical candidate in just 100 or 150 compounds, I wouldn’t have believed it. But that’s what happened, and that technology is a rare success story.

Something that really didn’t work nearly as well as initially advertised was the promise of X-ray structure-based drug design. When structures of ligands docked to proteins became more accessible, companies were founded on the basis that knowing the X-ray structure would lead directly to designing a ligand for that target. Most of those companies didn’t make it because people didn’t understand protein flexibility.

A lot of proteins, including just about all of the kinase targets, change

**“The success of fragment screening took me completely by surprise. If someone had told me 15 years ago [...] that screening compounds in the 100  $\mu\text{M}$  to [low] mM range could give you enough information to optimize and reach a clinical candidate in just 100 or 150 compounds, I wouldn’t have believed it. But that’s what happened, and that technology is a rare success story.”**

— *Chris Lipinski, Melior Discovery Inc.*

their shape when they bind a ligand. Any computational approach that can't take that into account is going to have a problem.

It is still a big issue, as it's very hard to predict what the eventual protein conformation will be when a protein structure comes in proximity [to] a small ligand. Part of the problem is that you have to run the computer simulations for a very long time to have enough time to see the movement of the protein, which on the time scale of a molecular dynamic simulation is very slow.

Although the idea was good the technology didn't work because not enough was known about the science. This is a general phenomenon in science. Everything looks better at an early stage before you have learned about the intricacies.

*SciBX*: What might be the next area of drug development in which *in silico* approaches will break through?

*CL*: One of the biggest challenges is the delivery of protein and RNA therapeutics. There are certain adjuvants that work partially, often by forming a complex between the compound and a cationic carrier.

*In silico* approaches could help with questions such as the compound characteristics that generate long enough residence time on the cell surface to enable cellular uptake and intracellular release. There is a

window of time before proteolytic enzymes and low pH destroy the agent, and using computer approaches to optimize the biophysics of that would be helpful.

In addition, *in silico* approaches could help in pharmacodynamics. Drugs such as antidepressants can take two to three weeks to have a measurable effect, but we know little about what's happening in that time.

There is a lot of interest in using systems biology to understand questions like this, especially at **NIH**. If we understood more about the behavior of biology networks, then our predictions about efficacy—which right now are absolutely horrible—would improve.

*SciBX*: Thank you very much for your time.

Fishburn, C.S. *SciBX* 6(46); doi:10.1038/scibx.2013.1309  
Published online Dec. 5, 2013

#### REFERENCES

1. Lipinski, C.A. *et al. Adv. Drug Deliv. Rev.* **23**, 3–25 (1997)
2. Lowe, D. *Lipinski's anchor. Corante* (Nov. 25, 2013)

#### COMPANIES AND INSTITUTIONS MENTIONED

**American Chemical Society**, Washington, D.C.  
**Melior Discovery Inc.**, Exton, Pa.  
**National Institutes of Health**, Bethesda, Md.  
**Pfizer Inc.** (NYSE:PFE), New York, N.Y.

## SciBX

**SciBX: Science–Business eXchange**—transform your ability to efficiently identify and evaluate new developments in science and technology that have commercial and investment potential within the biotechnology and pharmaceutical arena.

Subscribe today at **scibx.com**

# A gut feeling about butyrate

By Tracey Baas, Senior Editor

Inflammatory bowel disease and other inflammatory conditions of the gut have long been associated with imbalances in mucosal levels of microflora-produced short-chain fatty acids such as butyrate and propionate, but the underlying mechanisms were unknown. Work from two separate groups in the U.S. and Japan has now revealed how bacterial butyrate and propionate can drive the differentiation of anti-inflammatory T<sub>reg</sub> cells and thus promote mucosal health.<sup>1,2</sup>

Both teams are trying to find links between their findings and other immune-related conditions, such as autoimmune diseases and food allergies, while also looking into suitable therapeutic modalities for gut inflammatory conditions.

Butyrate insufficiency caused by low levels of butyrate-producing bacteria or downregulation of butyrate transporters in the colonic mucosa of patients with IBD has been implicated in IBD pathogenesis.<sup>3,4</sup>

In patients with IBD, enema treatment with butyrate or with a cocktail of short-chain fatty acids (SCFAs) ameliorates colonic inflammation via an unknown mode of action.<sup>5,6</sup>

A Japan team led by Hiroshi Ohno and a U.S. team led by Alexander Rudensky have independently elucidated one underlying mechanism.

Ohno is group director of the Laboratory for Epithelial Immunobiology at the **RIKEN Center for Integrative Medical Sciences**, and Rudensky is the immunology program chair and director of the **Ludwig Center for Cancer Immunotherapy at the Memorial Sloan-Kettering Cancer Center**.

The Japan team included researchers from **The University of Tokyo**, **Keio University** and the **Commonwealth Scientific and Industrial Research Organisation Food and Nutritional Sciences**.

Based on previous studies showing that T<sub>reg</sub> cells expressing *forkhead box P3* (*FOXP3*) play a key role in limiting inflammatory responses in the intestine,<sup>7</sup> both teams first set out to determine whether butyrate or other SCFAs would influence T<sub>reg</sub> cell differentiation *ex vivo*. Under T<sub>reg</sub> cell-inducing conditions, naïve mouse Cd4<sup>+</sup> T cells exposed to butyrate or fecal extracts obtained from mice with commensal bacteria exhibited greater T<sub>reg</sub> cell differentiation and higher numbers of *Foxp3*<sup>+</sup> T<sub>reg</sub> cells than Cd4<sup>+</sup> T cells exposed to other SCFAs or fecal extracts obtained from mice treated with antibiotics.

In the mice with commensal bacteria, the fecal extracts contained high levels of butyrate and propionate.

Next, both teams showed that in mice with normal gut flora, a diet containing butyrylated starch increased levels of colonic T<sub>reg</sub> cells compared with a diet containing acetylated or propionylated starch, indicating that butyrate plays a key role in microbe-mediated T<sub>reg</sub> cell induction. Importantly, butyrylated starch had no effect on antibiotic-treated or germ-free mice, suggesting that commensal bacteria are required for T<sub>reg</sub> cell induction.

Previous studies have established that butyrate can regulate gene expression epigenetically by inhibiting histone deacetylases

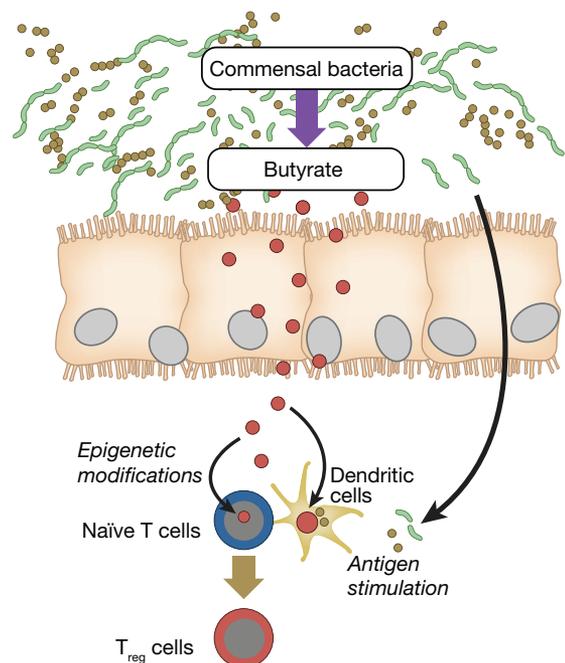
(HDACs),<sup>8,9</sup> and class IIa HDAC has been further reported to suppress T<sub>reg</sub> cell expansion.<sup>10,11</sup>

Both teams thus went on to show that under T<sub>reg</sub> cell-inducing conditions, butyrate led to increased histone H3 acetylation at *Foxp3* promoter and enhancer elements and correlated with increased *Foxp3* expression and T<sub>reg</sub> cell differentiation compared with no butyrate. These results established that butyrate contributes to T<sub>reg</sub> cell differentiation epigenetically (see Figure 1, “The commensal bacteria–butyrate–T<sub>reg</sub> cell axis of inflammatory regulation in the gut”).

Finally, the Japan researchers showed that a diet containing butyrylated starch prevented colitis in a mouse model of chronic intestinal inflammation. Diets containing normal starch did not prevent disease development. These disease-modifying results were seen in mice with normal levels of T<sub>reg</sub> cells but not in mice without T<sub>reg</sub> cells, indicating butyrate exerted its therapeutic activity through T<sub>reg</sub> cells.

Results from both teams were published in *Nature*.

“Thus far the precise mechanisms of how bacteria communicate with their hosts to promote immune functions have been poorly understood,”



**Figure 1. The commensal bacteria–butyrate–T<sub>reg</sub> cell axis of inflammatory regulation in the gut.** Certain commensal bacteria abundantly produce butyrate through fermentation of dietary fiber and other substrates. Two recent studies<sup>1,2</sup> found that butyrate promotes histone H3 lysine acetylation of the promoter and enhancer elements of *forkhead box P3* (*Foxp3*) in naïve mouse Cd4<sup>+</sup> T cells, eventually inducing the differentiation of T<sub>reg</sub> cells. T<sub>reg</sub> cells in turn contribute to mucosal health by regulating the inflammatory response in the gut.

*Ex vivo*, Arpaia *et al.* showed that greater levels of *Foxp3* acetylation and T<sub>reg</sub> cell differentiation could be achieved by coculturing butyrate-treated dendritic cells with naïve Cd4<sup>+</sup> T cells rather than directly treating naïve Cd4<sup>+</sup> T cells with butyrate. These results suggest that butyrate works through more than one immune cell population. (Figure based on Supplemental Figure 22 in ref. 1.)

said Carolin Daniel. “The present studies add to our understanding that microbes that metabolize dietary fiber can generate key fatty acids that enforce the induction of regulatory T cells.”

Daniel is junior group leader of immune tolerance in type 1 diabetes at the **Institute of Diabetes Research at Helmholtz Center Munich**.

“While our work may raise considerable interest in butyrate, elucidation of the modes of action and range of effects demand further investigation,” said Julie Clarke, an author on the Japan team’s manuscript and project leader for the Starplus Starch Technology in CSIRO’s Preventative Health Flagship. “More animal studies are required before any human disease intervention studies can be considered.”

Indeed, Diane Mathis told *SciBX*, “Only one colitis model has been studied and, being a quite artificial transfer model, I’d like to see the effect on better, especially spontaneous, disease models.” Mathis is a professor of microbiology and immunology at **Harvard Medical School**.

“I’d also like to see that these SCFAs can expand human T<sub>reg</sub> cells and under what conditions,” Mathis said. It would be helpful to characterize “what the SCFA landscape is like in humans, both in normal and diseased individuals.”

Previous studies from CSIRO and collaborators showed that butyrylated starch is effective at delivering significant quantities of butyrate to the large bowel of humans,<sup>12</sup> but those studies also showed that butyrylated starch

had limited effects on humoral immunity in healthy individuals.<sup>13</sup>

Daniel noted that the CSIRO studies call into question whether the application of butyrylated starch would be the approach of choice.

“One potential approach would be to feed specific substrates—prebiotics—that are suited to preferentially expand beneficial bacteria that can produce butyrate,” said Daniel. “Alternatively, one could think of isolating beneficial bacterial species and enrich them within the existing bacterial community of the host.”

### Further butyrate potential

Besides the prospects of harnessing butyrate as a therapeutic for IBD, the results open opportunities in a range of other inflammatory, T<sub>reg</sub> cell-dependent diseases.

“It would be interesting to see if the findings apply not only to mucosal inflammation in the intestine but also to organ-specific autoimmune diseases such as type 1 diabetes and sterile inflammation,” said Shimon Sakaguchi, a professor of experimental immunology at the **Immunology Frontier Research Center at Osaka University**.

Mathis was less sanguine, noting, “There is more and more evidence that T<sub>reg</sub> cells come in multiple flavors and that inflamed tissues have their own unique populations controlling autoimmunity and inflammatory responses. It is not yet clear to what extent the T<sub>reg</sub> cells generated in the gut or systemically under these conditions will be able to perform all surveillance and homeostatic functions. Butyrate-

induced T<sub>reg</sub> cell generation might work for some diseases, especially in the intestine, but not others.”

But Sakaguchi added, “Metabolites as well as environmental cues produced by commensal bacteria contain a wide range of immune modulators for innate and adaptive immune cells, so further detailed analyses will be needed to understand integrated immune responses and develop a measure to control the immune balance.”

“Regulatory T cells do play an essential role to avoid excessive inflammatory responses as well as autoimmunity. Therefore, the beneficial effects of butyrate could be applicable for the prevention and possibly also treatment of other autoimmune diseases or allergies—including food allergies—where T<sub>reg</sub> cells have been implied to be of relevance,” said Daniel. “With respect to inflammatory bowel disease it would be helpful to see specific outcomes in models for Crohn’s disease vs. ulcerative colitis—whether butyrate is equally beneficial in both diseases.”

Ohno’s team is planning to explore the role of butyrate and of colonic T<sub>reg</sub> cells in food allergy and to see if they can influence the experimental autoimmune encephalomyelitis (EAE) mouse model of multiple sclerosis (MS).

The team is also investigating alternative delivery methods to starch, but Ohno declined to give further details.

Rudensky’s team is now investigating how butyrate and colonic T<sub>reg</sub> cells play a role in autoimmune models of diabetes, colitis and rheumatoid arthritis (RA). The team is also looking into therapeutic modalities to bypass use of starch, but Rudensky declined to give further details.

The Japan team has filed a patent application covering the use of butyrate to induce differentiation of colonic T<sub>reg</sub> cells as a potential therapeutic for inflammatory, autoimmune and allergic diseases. The IP is unlicensed.

Acylation of starches and other fiber polysaccharides for the delivery of SCFAs to the large bowel is patented by CSIRO and is available for licensing.

The U.S. team has filed a provisional patent application protecting methods and compositions for modulating inflammation and treating T<sub>reg</sub> cell-associated diseases. The IP is available for licensing from the Office of Technology Development at the Memorial Sloan-Kettering Cancer Center.

**Baas, T. *SciBX* 6(46); doi:10.1038/scibx.2013.1310**

Published online Dec. 5, 2013

### REFERENCES

1. Furusawa, Y. *et al. Nature*; published online Nov. 13, 2013; doi:10.1038/nature12721  
**Contact:** Hiroshi Ohno, RIKEN Center for Integrative Medical Sciences, Kanagawa, Japan  
e-mail: [ohno@rcai.riken.jp](mailto:ohno@rcai.riken.jp)  
**Contact:** Koji Hase, same affiliation as above  
e-mail: [hase@ims.u-tokyo.ac.jp](mailto:hase@ims.u-tokyo.ac.jp)  
**Contact:** Shinji Fukuda, same affiliation as above  
e-mail: [sfukuda@sfc.keio.ac.jp](mailto:sfukuda@sfc.keio.ac.jp)
2. Arpaia, N. *et al. Nature*; published online Nov. 13, 2013; doi:10.1038/nature12726  
**Contact:** Alexander Y. Rudensky, Memorial Sloan-Kettering Cancer Center, New York, N.Y.  
e-mail: [rudenska@mskcc.org](mailto:rudenska@mskcc.org)
3. Thibault, R. *et al. Gastroenterology* **133**, 1916–1927 (2007)
4. Frank, D.N. *et al. Proc. Natl. Acad. Sci. USA* **104**, 13780–13785 (2007)
5. Scheppach, W. *et al. Gastroenterology* **103**, 51–56 (1992)
6. Harig, J.M. *et al. N. Engl. J. Med.* **320**, 23–28 (1989)
7. Josefowicz, S.Z. *et al. Nature* **482**, 395–399 (2012)

**“It would be interesting to see if the findings apply not only to mucosal inflammation in the intestine but also to organ-specific autoimmune diseases such as type 1 diabetes and sterile inflammation.”**

**—Shimon Sakaguchi,  
Immunology Frontier Research  
Center at Osaka University**

8. Candido, E.P.M. *et al. Cell* **14**, 105–113 (1978)
9. Davie, J.R. *J. Nutr.* **133**, 2485S–2493S (2003)
10. de Zoeten, E.F. *et al. Gastroenterology* **138**, 583–594 (2010)
11. Tao, R. *et al. Nat. Med.* **13**, 1299–1307 (2007)
12. Clarke, J.M. *et al. Am. J. Clin. Nutr.* **94**, 1276–1283 (2011)
13. West, N.P. *et al. Exerc. Immunol. Rev.* **19**, 102–119 (2013)

#### COMPANIES AND INSTITUTIONS MENTIONED

**Commonwealth Scientific and Industrial Research Organisation  
Food and Nutritional Sciences**, Adelaide, South Australia, Australia

**Harvard Medical School**, Boston, Mass.  
**Immunology Frontier Research Center at Osaka University**,  
Osaka, Japan  
**Institute of Diabetes Research at Helmholtz Center Munich**,  
Munich, Germany  
**Keio University**, Yamagata, Japan  
**Ludwig Center for Cancer Immunotherapy at the Memorial  
Sloan-Kettering Cancer Center**, New York, N.Y.  
**RIKEN Center for Integrative Medical Sciences**, Kanagawa, Japan  
**The University of Tokyo**, Tokyo, Japan



The Scientific Acumen of Nature Publishing Group  
*plus*  
The Business Intelligence of BioCentury Publications, Inc.  
*in a single publication*

**Can you afford not to subscribe?**  
Visit [scibx.com](http://scibx.com) for details on how to subscribe to SciBX

## This week in therapeutics

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

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

Indication	Target/marker/pathway	Summary	Licensing status	Publication and contact information
<b>Autoimmune disease</b>				
Colitis; inflammatory bowel disease (IBD); autoimmune disease	Forkhead box P3 (FOXP3)	<p>Cell culture and mouse studies suggest butyrylated compounds could be used to treat colitis or other autoimmune diseases. In mice fed starch derivatives, short-chain fatty acids produced by gut microbe fermentation of butyrylated starch, but not acetylated or propionylated starch, induced colonic T<sub>reg</sub> cell differentiation. In stimulated T cells, butyrate or a histone deacetylase (HDAC) inhibitor increased <i>Foxp3</i> expression and histone H3 acetylation at promoter and enhancer elements of <i>Foxp3</i> compared with no treatment. In a mouse model of chronic intestinal inflammation, oral butyrylated starch prevented colitis in mice with T<sub>reg</sub> cells but not in mice depleted of T<sub>reg</sub> cells. Next steps for the RIKEN group include determining if butyrate and colonic T<sub>reg</sub> cells are involved in food allergy.</p> <p>Next steps for the Memorial Sloan-Kettering Cancer Center group include developing HDAC inhibitors and short-chain fatty acids as therapeutic agents for IBD (<i>see A gut feeling about butyrate, page 7</i>).</p> <p><b>SciBX 6(46); doi:10.1038/scibx.2013.1311</b> Published online Dec. 5, 2013</p>	<p>For first study, patent application filed by RIKEN covering use of butyrate to induce differentiation of colonic T<sub>reg</sub> cells as a potential therapeutic for inflammatory, autoimmune and allergic diseases; unlicensed; butyrylated starch patented by the Commonwealth Scientific and Industrial Research Organisation (CSIRO); available for licensing; two CSIRO scientists were authors on the RIKEN manuscript</p> <p>For second study, patent application filed by MSKCC protecting methods and compositions for modulating inflammation and treating T<sub>reg</sub> cell-associated diseases; available for licensing</p>	<p>Furusawa, Y. <i>et al. Nature</i>; published online Nov. 13, 2013; doi:10.1038/nature12721 <b>Contact:</b> Hiroshi Ohno, RIKEN Center for Integrative Medical Sciences, Kanagawa, Japan e-mail: <a href="mailto:ohno@rci.riken.jp">ohno@rci.riken.jp</a> <b>Contact:</b> Koji Hase, same affiliation as above e-mail: <a href="mailto:hase@ims.u-tokyo.ac.jp">hase@ims.u-tokyo.ac.jp</a> <b>Contact:</b> Shinji Fukuda, same affiliation as above e-mail: <a href="mailto:sfukuda@sfc.keio.ac.jp">sfukuda@sfc.keio.ac.jp</a></p> <p>Arpaia, N. <i>et al. Nature</i>; published online Nov. 13, 2013; doi:10.1038/nature12726 <b>Contact:</b> Alexander Y. Rudensky, Memorial Sloan-Kettering Cancer Center, New York, N.Y. e-mail: <a href="mailto:rudenska@mskcc.org">rudenska@mskcc.org</a></p>
<b>Cancer</b>				
Bone metastases	MicroRNA-141 (miR-141); miR-219	<p>Cell culture and mouse studies suggest miR-141 and miR-219 could help prevent bone metastases. In cultured pre-osteoclasts, conditioned medium from highly metastatic tumors induced osteoclast differentiation, whereas medium from weakly metastatic tumors did not. miRNA profiling identified 5 miRNAs, including miR-141 and miR-219, that were downregulated during osteoclast differentiation. Overexpression of any of the miRNAs in cultured pre-osteoclasts decreased conditioned medium-induced differentiation compared with normal expression. In mouse xenograft models of bone metastasis, miR-141 and miR-219 decreased metastatic tumor burden compared with saline.</p> <p>Next steps include improving the targeting of miRNA mimics to bone in mice.</p> <p><b>SciBX 6(46); doi:10.1038/scibx.2013.1312</b> Published online Dec. 5, 2013</p>	Patent application filed; available for licensing	<p>Ell, B. <i>et al. Cancer Cell</i>; published online Oct. 14, 2013; doi:10.1016/j.ccr.2013.09.008 <b>Contact:</b> Yibin Kang, Princeton University, Princeton, N.J. e-mail: <a href="mailto:ykang@princeton.edu">ykang@princeton.edu</a></p>

## This week in therapeutics (continued)

Indication	Target/marker/pathway	Summary	Licensing status	Publication and contact information
Breast cancer; pancreatic cancer	DNA	<p>Mouse and cell culture studies suggest a mitochondria-targeted triphenylphosphonium derivative of the nitrogen mustard chlorambucil could help treat breast and pancreatic cancers. In a panel of breast and pancreatic cancer cell lines, the compound showed more potent anticancer activity than chlorambucil. In a mouse xenograft model of human pancreatic cancer, the compound decreased tumor growth compared with vehicle. Next steps could include developing optimized derivatives and evaluating them in additional animal models of breast and pancreatic cancers.</p> <p><b>SciBX 6(46); doi:10.1038/scibx.2013.1313</b>  <b>Published online Dec. 5, 2013</b></p>	Patent and licensing status unavailable	<p>Millard, M. <i>et al. J. Med. Chem.</i>; published online Oct. 22, 2013; doi:10.1021/jm4012438  <b>Contact:</b> Nouri Neamati, University of Michigan, Ann Arbor, Mich.  e-mail: <a href="mailto:neamati@umich.edu">neamati@umich.edu</a>  <b>Contact:</b> Bogdan Z. Olenyuk, University of Southern California, Los Angeles, Calif.  e-mail: <a href="mailto:bogdan@usc.edu">bogdan@usc.edu</a></p>
Cancer	Toll-like receptor 9 (TLR9); signal transducer and activator of transcription 3 (STAT3)	<p>Mouse studies suggest inhibitors of TLR9 or STAT3 could help prevent tumor recurrence after radiation therapy. In radiation-treated mice bearing melanoma, bladder or colorectal tumors, <i>Tlr9</i> knockout decreased activation of Stat3 in tumor-infiltrating myeloid cells compared with no knockout, thereby inhibiting tumor revascularization and tumor regrowth. In wild-type mice bearing those tumor types, radiation and either a TLR9 antagonist or <i>Stat3</i> small interfering RNA increased the time to tumor regrowth compared with radiation or targeted therapy alone. Ongoing work includes confirming the finding in tissue samples from patients with prostate cancer undergoing radiation therapy.</p> <p>Isis Pharmaceuticals Inc. and AstraZeneca plc have ISIS-STAT3Rx (AZD9150), an antisense inhibitor of STAT3, in Phase I/II testing to treat solid and blood cancers.</p> <p>Otsuka Pharmaceutical Co. Ltd. has OPB-31121, an inhibitor of STAT3 phosphorylation, in Phase I trials to treat solid tumors.</p> <p>Dynavax Technologies Corp. and GlaxoSmithKline plc have DV1179, an inhibitor of TLR9 and TLR7, in Phase I testing to treat systemic lupus erythematosus (SLE) and autoimmune and inflammatory diseases.</p> <p><b>SciBX 6(46); doi:10.1038/scibx.2013.1314</b>  <b>Published online Dec. 5, 2013</b></p>	Patent application filed by City of Hope; available for licensing	<p>Gao, C. <i>et al. Cancer Res.</i>; published online Oct. 23, 2013; doi:10.1158/0008-5472.CAN-13-1314  <b>Contact:</b> Marcin Kortylewski, Beckman Research Institute at City of Hope, Duarte, Calif.  e-mail: <a href="mailto:mkortylewski@coh.org">mkortylewski@coh.org</a></p>
Cancer	Tubulin	<p><i>In vitro</i> and mouse studies have identified aryloxazole-based tubulin inhibitors that could help treat cancer. Screening of a small molecule library and <i>in vitro</i> testing of aryloxazole analogs identified several lead compounds that inhibited tubulin polymerization and reduced the viability of human leukemia, lung cancer and colorectal cancer cell lines at nanomolar IC<sub>50</sub> values. In mice bearing xenograft colorectal tumors, one lead compound decreased tumor growth compared with no treatment. Future studies could include optimizing and testing the lead compounds in other tumor models.</p> <p><b>SciBX 6(46); doi:10.1038/scibx.2013.1315</b>  <b>Published online Dec. 5, 2013</b></p>	Patent and licensing status unavailable	<p>Choi, M.J. <i>et al. J. Med. Chem.</i>; published online Oct. 27, 2013; doi:10.1021/jm400840p  <b>Contact:</b> GhilSoo Nam, Korea Institute of Science and Technology, Seoul, South Korea  e-mail: <a href="mailto:gsnam@kist.re.kr">gsnam@kist.re.kr</a>  <b>Contact:</b> Ae Nim Pae, same affiliation as above  e-mail: <a href="mailto:anpae@kist.re.kr">anpae@kist.re.kr</a></p>

## This week in therapeutics (continued)

Indication	Target/marker/pathway	Summary	Licensing status	Publication and contact information
Chronic myelogenous leukemia (CML)	BCR-ABL tyrosine kinase; macrophage inflammatory protein-1 $\alpha$ (CCL3; MIP1A)	<p>Mouse studies suggest inhibiting CCL3 signaling could help treat CML. In a newly developed, nonirradiated mouse model of CML using BCR-ABL-expressing, leukemia-initiating cells, <i>Ccl3</i> knockout delayed disease relapse following cessation of Gleevec imatinib therapy and increased survival compared with no knockout. Next steps include studies to identify progenitor cell subsets that compete with leukemia-initiating cells and to understand how such cells are maintained in the bone marrow niche. Novartis AG markets Gleevec to treat CML and gastrointestinal stromal tumors.</p> <p><b>SciBX 6(46); doi:10.1038/scibx.2013.1316</b>  <b>Published online Dec. 5, 2013</b></p>	Patent application filed; licensing details available from Kanazawa University	<p>Baba, T. <i>et al. J. Exp. Med.</i>; published online Oct. 28, 2013; doi:10.1084/jem.20130112  <b>Contact:</b> Tomohisa Baba, Kanazawa University, Ishikawa, Japan  e-mail: <a href="mailto:sergenti@staff.kanazawa-u.ac.jp">sergenti@staff.kanazawa-u.ac.jp</a></p>
Hodgkin's lymphoma	Discoidin domain receptor tyrosine kinase 1 (DDR1)	<p><i>In vitro</i> studies suggest inhibiting DDR1 could help increase the efficacy of chemotherapeutics in Hodgkin's lymphoma. In Hodgkin's lymphoma cells, collagen from the tumor microenvironment induced DDR1 phosphorylation, and small interfering RNA against <i>DDR1</i> increased cell death of the collagen-treated cells compared with control siRNA. In collagen-treated Hodgkin's lymphoma cells, overexpression of DDR1 protected the cells from etoposide-induced cell death. Next steps could include testing DDR1 inhibition in mouse models using broad-spectrum receptor tyrosine kinase inhibitors such as Sprycel dasatinib and Tassigna nilotinib in combination with chemotherapeutics. Bristol-Myers Squibb Co. and Otsuka Pharmaceutical Co. Ltd. market Sprycel to treat chronic myelogenous leukemia (CML) and acute lymphoblastic leukemia (ALL). Novartis AG markets Tassigna to treat CML. Etoposide is a generic topoisomerase inhibitor chemotherapeutic.</p> <p><b>SciBX 6(46); doi:10.1038/scibx.2013.1317</b>  <b>Published online Dec. 5, 2013</b></p>	Patent and licensing status unavailable	<p>Cader, F.Z. <i>et al. Blood</i>; published online Oct. 17, 2013; doi:10.1182/blood-2013-04-499004  <b>Contact:</b> Fathima Zumla Cader, University of Birmingham, Birmingham, U.K.  e-mail: <a href="mailto:f.z.cader@bham.ac.uk">f.z.cader@bham.ac.uk</a></p>
Prostate cancer	UDP glucuronosyltransferase 2 family polypeptide B15 (UGT2B15)	<p>Patient and cell culture studies suggest activating UGT2B15 could help treat prostate cancer. In samples from patients with prostate cancer receiving androgen deprivation therapy, UGT2B15 levels were higher than those in patients not receiving the therapy. In cultured prostate cancer cell lines, androgen receptor (AR) antagonists led to an AR-dependent decrease in UGT2B15 expression and activity compared with no treatment. Also in the cells, <i>UGT2B15</i> knockdown decreased the antiproliferative effects of AR antagonists compared with no knockdown. Next steps include finding selective activators of UGT2B15 and generating transgenic mouse models expressing human <i>UGT2B15</i>.</p> <p><b>SciBX 6(46); doi:10.1038/scibx.2013.1318</b>  <b>Published online Dec. 5, 2013</b></p>	Unpatented; licensing status not applicable	<p>Grosse, L. <i>et al. Cancer Res.</i>; published online Oct. 11, 2013; doi:10.1158/0008-5472.CAN-13-1462  <b>Contact:</b> Olivier Barbier, Laval University, Quebec City, Quebec, Canada  e-mail: <a href="mailto:olivier.barbier@crchul.ulaval.ca">olivier.barbier@crchul.ulaval.ca</a></p>

## This week in therapeutics (continued)

Indication	Target/marker/ pathway	Summary	Licensing status	Publication and contact information
<b>Cardiovascular disease</b>				
Hypertension	Fatty acid amide hydrolase (FAAH)	<p>Mouse studies suggest inhibiting anandamide signaling through FAAH could help treat or prevent pulmonary hypertension. In isolated, perfused lungs from mice, the endocannabinoid anandamide increased pulmonary vascular tone compared with vehicle. In mice, increased hypoxia-induced pulmonary hypertension was associated with increased levels of anandamide and Faah-dependent anandamide metabolites in the lung. Also in mice, <i>Faah</i> knockout or a FAAH antagonist prevented hypoxia-induced pulmonary hypertension. Next steps could include evaluating additional FAAH antagonists in animal models of pulmonary hypertension. Vernalis plc has V158866, a small molecule inhibitor of FAAH, in Phase II trials to treat pain.</p> <p><b>SciBX 6(46); doi:10.1038/scibx.2013.1319</b> Published online Dec. 5, 2013</p>	Patent and licensing status unavailable	<p>Wenzel, D. <i>et al. Proc. Natl. Acad. Sci. USA</i>; published online Oct. 28, 2013; doi:10.1073/pnas.1308130110</p> <p><b>Contact:</b> Bernd K. Fleischmann, University of Bonn, Bonn, Germany e-mail: <a href="mailto:bernd.fleischmann@uni-bonn.de">bernd.fleischmann@uni-bonn.de</a></p>
<b>Endocrine/metabolic disease</b>				
Diabetes; obesity	Adiponectin (ADIPOQ); adiponectin receptor 1 (ADIPOR1); ADIPOR2	<p>Mouse studies suggest a dual ADIPOR1 and ADIPOR2 agonist could help treat obesity and type 2 diabetes. <i>In vitro</i> screening of a small molecule library identified an agonist of ADIPOR1 and ADIPOR2 that bound the receptors with low micromolar affinities. In mouse models of obesity and diabetes, the compound decreased plasma levels of triglycerides and glucose, decreased insulin resistance and increased glucose tolerance compared with vehicle, without affecting weight or food intake. In obese and diabetic mice fed a high-fat diet, the compound increased lifespan compared with no treatment. Planned work includes optimizing and testing the compound in the obesity and diabetes models.</p> <p><b>SciBX 6(46); doi:10.1038/scibx.2013.1320</b> Published online Dec. 5, 2013</p>	Patented by The University of Tokyo; licensing status undisclosed	<p>Okada-Iwabu, M. <i>et al. Nature</i>; published online Oct. 30, 2013; doi:10.1038/nature12656</p> <p><b>Contact:</b> Toshimasa Yamauchi, The University of Tokyo, Tokyo, Japan e-mail: <a href="mailto:tyama-u-tky@umin.net">tyama-u-tky@umin.net</a></p>
Dyslipidemia; metabolic disease	Patatin-like phospholipase domain containing 2 (PNPLA2; ATGL)	<p><i>In vitro</i> and mouse studies have identified an inhibitor of ATGL that might help treat dyslipidemia and metabolic disorders. Lead optimization of lipase inhibitors yielded a compound that inhibited ATGL with an <math>IC_{50}</math> of about 700 nM. In lysates from ATGL-overexpressing <i>Escherichia coli</i> and mouse white adipose tissue, the ATGL inhibitor decreased triglyceride hydrolase activity compared with vehicle. In fasted mice, the inhibitor produced a time- and concentration-dependent decrease in the release of fatty acids and glycerol compared with vehicle. Next steps include optimizing the inhibitor for human ATGL and testing it in diet-induced models of metabolic disease.</p> <p><b>SciBX 6(46); doi:10.1038/scibx.2013.1321</b> Published online Dec. 5, 2013</p>	Patent application filed; available for licensing	<p>Mayer, N. <i>et al. Nat. Chem. Biol.</i>; published online Oct. 6, 2013; doi:10.1038/nchembio.1359</p> <p><b>Contact:</b> Rolf Breinbauer, Graz University of Technology, Graz, Austria e-mail: <a href="mailto:breinbauer@tugraz.at">breinbauer@tugraz.at</a></p> <p><b>Contact:</b> Robert Zimmermann, same affiliation as above e-mail: <a href="mailto:robert.zimmermann@uni-graz.at">robert.zimmermann@uni-graz.at</a></p>

## This week in therapeutics (continued)

Indication	Target/marker/ pathway	Summary	Licensing status	Publication and contact information
<b>Infectious disease</b>				
Chagas disease; leishmaniasis	Tubulin	<i>In vitro</i> and mouse studies have identified a class of tubulin inhibitors that could help treat parasitic infections. Chemical synthesis and <i>in vitro</i> testing of sulfonamide analogs identified several tubulin inhibitors that killed <i>Trypanosoma cruzi</i> and four <i>Leishmania</i> species at low nanomolar IC <sub>50</sub> values. In a mouse model of Chagas disease, one lead compound decreased blood levels of <i>T. cruzi</i> by 72% and increased survival compared with no treatment. In a mouse model of leishmaniasis, another lead compound decreased the burden of <i>L. infantum</i> in the spleen and liver by 96% compared with no treatment. Next steps could include lead optimization of the two compounds.	Patent and licensing status unavailable	Galiana-Roselló, C. <i>et al. J. Med. Chem.</i> ; published online Oct. 23, 2013; doi:10.1021/jm4006127 <b>Contact:</b> M. Eugenia González-Rosende, Cardinal Herrera University, Valencia, Spain e-mail: <a href="mailto:eugenia@uch.ceu.es">eugenia@uch.ceu.es</a>
Dengue fever	Dengue virus envelope protein E (DENV_gp1)	<i>In vitro</i> studies have identified residues of the dengue virus envelope protein that could be targeted to treat dengue fever. In cultured human cells, infection with dengue virus clones containing point mutations in each of 390 DENV_gp1 ectodomain residues identified 18 residues required for viral infectivity that did not structurally impair the protein. Mapping the residues to seven known conformational folding structures of the protein showed that the critical residues were located near the protein fusion loop, a conserved region at the interface of envelope protein domain interactions. Next steps include evaluating how mAbs targeting envelope protein interact with the critical residue regions. Altravax Inc. has a vaccine against DENV_gp1 in preclinical testing for dengue fever.	Patents filed by Integral Molecular Inc. covering the mutagenesis method to create the mutations and the envelope protein-targeted mAbs; licensing status undisclosed	Christian, E.A. <i>et al. Proc. Natl. Acad. Sci. USA</i> ; published online Oct. 24, 2013; doi:10.1073/pnas.1310962110 <b>Contact:</b> Benjamin J. Doranz, Integral Molecular Inc., Philadelphia, Pa. e-mail: <a href="mailto:bdoranz@integralmolecular.com">bdoranz@integralmolecular.com</a>
HIV/AIDS	HIV gp120	Nonhuman primate studies suggest the broadly neutralizing, anti-HIV gp120 mAb PGT121 could be used to treat HIV infection. In rhesus macaques chronically infected with a pathogenic simian-human immunodeficiency virus (SHIV), PGT121 led to transient virological control in four of four macaques and longer-term control in one of four macaques. In the monkeys, PGT121 decreased viral RNA in plasma and proviral DNA in blood and tissues and increased T cell responses and functionality compared with a control antibody. Next steps include testing the mAb in combination with antiretroviral therapies in SHIV-infected rhesus macaques. The International AIDS Vaccine Initiative (IAVI) and Theraclone Sciences Inc. are collaborating on PGT121 and additional anti-HIV antibodies; IAVI retains rights to develop vaccines based on these findings, whereas Theraclone retains rights to develop therapeutics based on these antibodies.	Patent status undisclosed; PGT121 available for partnering and licensing from Theraclone Sciences	Barouch, D.H. <i>et al. Nature</i> ; published online Oct. 30, 2013; doi:10.1038/nature12744 <b>Contact:</b> Dan H. Barouch, Beth Israel Deaconess Medical Center and Harvard Medical School, Boston, Mass. e-mail: <a href="mailto:dbarouch@bidmc.harvard.edu">dbarouch@bidmc.harvard.edu</a>
		<b>SciBX 6(46); doi:10.1038/scibx.2013.1322</b> <b>Published online Dec. 5, 2013</b>		
		<b>SciBX 6(46); doi:10.1038/scibx.2013.1323</b> <b>Published online Dec. 5, 2013</b>		
		<b>SciBX 6(46); doi:10.1038/scibx.2013.1324</b> <b>Published online Dec. 5, 2013</b>		

## This week in therapeutics (continued)

Indication	Target/marker/ pathway	Summary	Licensing status	Publication and contact information
HIV/AIDS	HIV gp120	Nonhuman primate studies suggest combining the anti-HIV gp120 mAbs 3BNC117 and 10-1074 could help treat HIV infection. In rhesus macaques chronically infected with a pathogenic simian-human immunodeficiency virus (SHIV) with low CD4 <sup>+</sup> T cell levels, co-delivery of 3BNC117 and 10-1074 prolonged the time to virus rebound to three to five weeks, whereas individual antibodies only prolonged the time to virus rebound by four to seven days. Next steps include clinical trials with the antibodies to treat patients infected with HIV.	Patent application filed; unlicensed	Shingai, M. <i>et al. Nature</i> ; published online Oct. 30, 2013; doi:10.1038/nature12746 <b>Contact:</b> Malcolm A. Martin, National Institute of Allergy and Infectious Diseases, Bethesda, Md. e-mail: <a href="mailto:mmartin@niaid.nih.gov">mmartin@niaid.nih.gov</a>
<b>Musculoskeletal disease</b>				
Musculoskeletal disease	TNF-like weak inducer of apoptosis (TWEAK)	<i>In vitro</i> and mouse studies suggest inhibiting TWEAK could promote muscle regeneration after injury. In <i>Tweak</i> <sup>-/-</sup> mice, the number of self-renewing satellite cells in muscle after injury was higher than that in wild-type controls. In primary satellite cells from the mice, Tweak decreased the number of self-renewing satellite cells compared with no treatment. Next steps could include testing the effects of TWEAK inhibition on muscle regeneration. Biogen Idec Inc. has BIIB023, a mAb against TWEAK, in Phase II trials to treat lupus nephritis.	Patent and licensing status unavailable	Ogura, Y. <i>et al. J. Biol. Chem.</i> ; published online Oct. 22, 2013; doi:10.1074/jbc.M113.517300 <b>Contact:</b> Ashok Kumar, University of Louisville School of Medicine, Louisville, Ky. e-mail: <a href="mailto:ashok.kumar@louisville.edu">ashok.kumar@louisville.edu</a>
<b>Neurology</b>				
Parkinson's disease (PD)	$\alpha$ -Synuclein (SNCA); NEDD4 family E3 ubiquitin protein ligase (RSP5); neural precursor cell expressed developmentally downregulated 4 (NEDD4; NEDD4-1)	<i>In vitro</i> and <i>ex vivo</i> studies identified an <i>N</i> -arylbenzimidazole (NAB) that could help treat PD. In a yeast-based screen, the NAB reversed SNCA pathology, including reactive oxygen species (ROS) generation, vesicular trafficking disruption and SNCA foci formation. In rat and patient-derived <i>ex vivo</i> neuronal models of PD, the most potent NAB decreased SNCA pathology compared with vehicle by promoting RSP5- and NEDD4-mediated vesicular trafficking. In cortical neurons derived from patient induced pluripotent stem (iPS) cells expressing mutant SNCA, the NAB also corrected protein nitration and endoplasmic reticulum-associated degradation. Next steps could include testing the NAB in animal models of PD.	Patent and licensing status unavailable for both studies	Tardiff, D.F. <i>et al. Science</i> ; published online Oct. 24, 2013; doi:10.1126/science.1245321 Chung, C.Y. <i>et al. Science</i> ; published online Oct. 24, 2013; doi:10.1126/science.1245296 <b>Contact:</b> Susan Lindquist, Whitehead Institute for Biomedical Research, Cambridge, Mass. e-mail: <a href="mailto:lindquist_admin@wi.mit.edu">lindquist_admin@wi.mit.edu</a>

## This week in therapeutics (continued)

Indication	Target/marker/ pathway	Summary	Licensing status	Publication and contact information
<b>Various</b>				
Inflammation; thrombosis	Factor Xa; factor XIa; kallikrein	<i>In vitro</i> and rodent studies suggest desmolaris, a protein from vampire bat saliva, could help treat inflammation and thrombosis. A series of <i>in vitro</i> assays identified desmolaris in vampire bat saliva as a slow, tight, noncompetitive inhibitor of factor Xa and XIa and a partial inhibitor of kallikrein. In mouse models of thrombosis and thromboembolism, desmolaris decreased arterial occlusion and increased survival compared with saline. In mice, injection of desmolaris-treated factor Xa decreased paw inflammation compared with injection of saline-treated factor Xa. Next steps include establishing a partnership for further preclinical and clinical development of desmolaris.	Patent application filed; available for licensing from the NIH <b>Contact:</b> Charlene Sydnor, National Institutes of Health (NIH), Bethesda, Md. e-mail: <a href="mailto:sydnorc@od.nih.gov">sydnorc@od.nih.gov</a>	Ma, D. <i>et al. Blood</i> ; published online Oct. 24, 2013; doi:10.1182/blood-2013-08-517474 <b>Contact:</b> Ivo M.B. Francischetti, National Institutes of Health (NIH), Bethesda, Md. e-mail: <a href="mailto:ifrancischetti@niaid.nih.gov">ifrancischetti@niaid.nih.gov</a>
<b>SciBX 6(46); doi:10.1038/scibx.2013.1328 Published online Dec. 5, 2013</b>				
Liver disease, pulmonary fibrosis	Integrin $\alpha_v$ (CD51)	Studies in mice suggest a small molecule inhibitor of CD51 could help treat fibrosis. In mouse models of liver, lung and kidney fibrosis, <i>Cd51</i> knockout in myofibroblasts prevented fibrosis. In mouse models of fibrosis, a small molecule inhibitor of <i>Cd51</i> decreased fibrosis progression in liver and lung compared with an inactive enantiomer. Next steps include identifying CD51 dimerization partners in profibrotic integrin complexes and assessing cellular and transcriptional changes resulting from CD51 inhibition. The CD51 inhibitor was developed by new company Antegrin Therapeutics LLC ( <i>see Targeting fibrotic integrin</i> , page 1).	Patent application for CD51 inhibitor and related inhibitors filed by Antegrin Therapeutics; patent application filed by the University of California, San Francisco covering identification of CD51-containing integrins; available for licensing	Henderson, N.C. <i>et al. Nat. Med.</i> ; published online Nov. 10, 2013; doi:10.1038/nm.3282 <b>Contact:</b> Dean Sheppard, University of California, San Francisco, Calif. e-mail: <a href="mailto:dean.sheppard@ucsf.edu">dean.sheppard@ucsf.edu</a> <b>Contact:</b> Neil C. Henderson, The University of Edinburgh, Edinburgh, U.K. e-mail: <a href="mailto:henderson@ed.ac.uk">henderson@ed.ac.uk</a>
<b>SciBX 6(46); doi:10.1038/scibx.2013.1329 Published online Dec. 5, 2013</b>				

## SciBX: Science–Business eXchange

Kick-start your knowledge management—and leave your competitors behind...

Can you afford not to subscribe?

Visit [scibx.com](http://scibx.com) for details on how to subscribe to SciBX

## This week in techniques

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

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

Approach	Summary	Licensing status	Publication and contact information
<b>Assays &amp; screens</b>			
<i>In vitro</i> screening for genetic signatures associated with sensitivity to targeted cancer therapeutics	<p>Combined genetic and chemical screening of lung cancer cells for altered genetic signatures could reveal sensitivity to therapeutic candidates. The screening approach involved identifying small molecule inhibitors and small interfering RNAs that reduced growth of cancer cells from a patient tumor sample but had no effect on growth of normal cells from the same patient. The small molecules and siRNAs were then tested in a panel of 91 non-small cell lung cancer (NSCLC) cell lines to identify common signatures of sensitivity. <i>K-Ras</i> (<i>KRAS</i>) and <i>serine/threonine kinase 11</i> (<i>STK11</i>; <i>LKB1</i>) mutations correlated with sensitivity to knockdown of <i>constitutive photomorphogenic 1</i> (<i>COP1</i>; <i>RFWD2</i>). In addition, a seven-gene expression signature correlated with sensitivity to an indolotriazine-based compound. Next steps could include using this approach to identify sensitivity to therapeutics in additional cancer types.</p> <p><b>SciBX 6(46); doi:10.1038/scibx.2013.1330</b>  <b>Published online Dec. 5, 2013</b></p>	Patent and licensing status unavailable	<p>Kim, H.S. <i>et al. Cell</i>; published online Oct. 24, 2013;  doi:10.1016/j.cell.2013.09.041  <b>Contact:</b> Michael A. White, The University of Texas Southwestern Medical Center, Dallas, Texas  e-mail:  <a href="mailto:michael.white@utsouthwestern.edu">michael.white@utsouthwestern.edu</a></p>
Leukemia-stroma coculture system to screen for selective inhibitors of leukemia stem cells (LSCs)	<p>A leukemia-stroma coculture system could be used in high throughput screens for compounds that selectively inhibit LSCs. The 384-well system cocultures primary, LSC-enriched cell populations with bone marrow stromal cells and uses an automated machine-learning algorithm to identify compounds that could inhibit a behavior called cobblestone area formation. The system plus a series of safety filters were used to screen a library of 14,718 compounds, which yielded 15 top hits that selectively inhibited LSCs over normal hematopoietic stem and progenitor cells (HSPCs) and lacked toxicity against two bone marrow stromal cell types. Follow-up validation studies on one of the top screening hits, the generic HMG-CoA reductase inhibitor lovastatin, showed that the drug selectively killed LSCs over normal HSPCs in culture and prevented the development of leukemia in a mouse model. Next steps could include evaluating lovastatin and other top screening hits in combination with existing leukemia drugs in animal models.</p> <p><b>SciBX 6(46); doi:10.1038/scibx.2013.1331</b>  <b>Published online Dec. 5, 2013</b></p>	Patent and licensing status unavailable	<p>Hartwell, K.A. <i>et al. Nat. Chem. Biol.</i>; published online Oct. 27, 2013;  doi:10.1038/nchembio.1367  <b>Contact:</b> Todd R. Golub, Broad Institute of MIT and Harvard, Cambridge, Mass.  e-mail:  <a href="mailto:golub@broadinstitute.org">golub@broadinstitute.org</a>  <b>Contact:</b> Benjamin L. Ebert, same affiliation as above  e-mail:  <a href="mailto:bebert@partners.org">bebert@partners.org</a>  <b>Contact:</b> Stuart L. Schreiber, same affiliation as above  e-mail:  <a href="mailto:stuart_schreiber@harvard.edu">stuart_schreiber@harvard.edu</a>  <b>Contact:</b> David T. Scadden, same affiliation as above  e-mail:  <a href="mailto:dscadden@mgh.harvard.edu">dscadden@mgh.harvard.edu</a>  <b>Contact:</b> Malcolm A.S. Moore, Memorial Sloan-Kettering Cancer Center, New York, N.Y.  e-mail:  <a href="mailto:m-moore@ski.mskcc.org">m-moore@ski.mskcc.org</a></p>

## This week in techniques (continued)

Approach	Summary	Licensing status	Publication and contact information
Radiohalogen label for improved tracking of therapeutic antibodies <i>in vivo</i>	<p>An <sup>125</sup>I-based radiohalogen probe with improved cell retention could aid preclinical biodistribution studies of therapeutic mAbs. A drawback of using iodine radionuclides to label and track mAbs is rapid diffusion of the label from cells following endocytosis and lysosomal degradation. To improve cellular retention of the label, an <sup>125</sup>I-labeled, 4-hydroxy-3-iodophenyl (HIP)-modified 1,4,7,10-tetraazacyclododecane-1,4,7,10-tetraacetic acid (DOTA) group was synthesized and attached to the human HER2 (EGFR2; ErbB2; neu) antibody Herceptin trastuzumab. In a mouse xenograft model of breast cancer, the labeled Herceptin had higher retention levels than <sup>125</sup>I tyrosine-modified Herceptin, although comparable levels of the antibodies were detected in plasma. Next steps include generating further derivatives of the probe and evaluating the labeling method with additional therapeutic or diagnostic antibodies. Roche and its Genentech Inc. unit market Herceptin, a humanized mAb against HER2, to treat breast and gastric cancer.</p> <p><b>SciBX 6(46); doi:10.1038/scibx.2013.1332</b> Published online Dec. 5, 2013</p>	Patent application filed; may be available for partnerships and collaborations	<p>Boswell, C.A. <i>et al. J. Med. Chem.</i>; published online Oct. 16, 2013; doi:10.1021/jm401365h</p> <p><b>Contact:</b> C. Andrew Boswell, Genentech Research and Early Development, South San Francisco, Calif. e-mail: <a href="mailto:boswell.andy@gene.com">boswell.andy@gene.com</a></p>
<b>Disease models</b>			
Mouse model of intrahepatic cholangiocarcinoma (ICC)	<p>Orthotopic allograft mouse models of ICC could be used to validate drivers of the disease. In mice, intrahepatic implantation of mouse liver progenitor cells expressing mutant forms of p53 and K-Ras (KRAS) caused development of tumors with histological features of ICC, including stromal cell infiltration. In the model, induced expression of a fusion gene containing <i>Golgi-associated PDZ and coiled-coil motif containing (GOPC; FIG)</i> linked to <i>c-ros proto-oncogene 1 receptor tyrosine kinase (ROS1)</i>, which has been found in a subset of patients with ICC, accelerated tumor growth. In the mouse model with established tumors that expressed the fusion gene, turning off its expression prevented further tumor growth. Next steps could include using the model to validate additional ICC targets.</p> <p><b>SciBX 6(46); doi:10.1038/scibx.2013.1333</b> Published online Dec. 5, 2013</p>	Patent and licensing status unavailable	<p>Saborowski, A. <i>et al. Proc. Natl. Acad. Sci. USA</i>; published online Oct. 23, 2013; doi:10.1073/pnas.1311707110</p> <p><b>Contact:</b> Scott W. Lowe, Memorial Sloan-Kettering Cancer Center, New York, N.Y. e-mail: <a href="mailto:lowes@mskcc.org">lowes@mskcc.org</a></p>
<b>Drug delivery</b>			
Nanoparticle-mediated co-delivery of small interfering RNA and cisplatin prodrug	<p>Engineered, self-assembling nanoparticles that co-deliver siRNA and a cisplatin prodrug could improve cancer chemotherapy response. The nanoparticles, consisting of a biodegradable diblock copolymer and a self-synthesized cationic lipid, are loaded with a cisplatin prodrug and siRNAs targeting REV1 and REV3-like catalytic subunit of DNA polymerase-<math>\zeta</math> (REV3L). In mouse xenograft models of human prostate cancer, siRNA- and prodrug-loaded nanoparticles led to decreased tumor growth and increased survival compared with nanoparticles loaded with the prodrug or siRNAs alone. Next steps could include evaluating delivery of different siRNA and drug payload combinations with the nanoparticles.</p> <p><b>SciBX 6(46); doi:10.1038/scibx.2013.1334</b> Published online Dec. 5, 2013</p>	Patent and licensing status undisclosed	<p>Xu, X. <i>et al. Proc. Natl. Acad. Sci. USA</i>; published online Oct. 28, 2013; doi:10.1073/pnas.1303958110</p> <p><b>Contact:</b> Omid C. Farokhzad, Harvard Medical School, Boston, Mass. e-mail: <a href="mailto:ofarokhzad@zeus.bwh.harvard.edu">ofarokhzad@zeus.bwh.harvard.edu</a></p> <p><b>Contact:</b> Graham C. Walker, Massachusetts Institute of Technology, Cambridge, Mass. e-mail: <a href="mailto:gwalker@mit.edu">gwalker@mit.edu</a></p>
<b>Drug platforms</b>			
Expandable and transplantable fetal intestinal progenitors with colon-regenerative potential	<p>Intestinal progenitor cells with fetal characteristics could be used to repair injured colon epithelium. <i>Ex vivo</i>, intestinal progenitors isolated from human fetal intestinal tissue or generated from induced pluripotent stem (iPS) cells formed fetal enterospheres that could be maintained and propagated for over two months. In mouse studies, an analogous cell population was differentiated <i>ex vivo</i> into intestinal epithelial progeny and used in a mouse model of colonic injury to engraft and form intestinal epithelial structures. Next steps include upscaling the procedure using human iPS cells and testing human enterospheres in a mouse model of colitis.</p> <p><b>SciBX 6(46); doi:10.1038/scibx.2013.1335</b> Published online Dec. 5, 2013</p>	Unpatented; unavailable for licensing	<p>Fordham, R.P. <i>et al. Cell Stem Cell</i>; published online Oct. 17, 2013; doi:10.1016/j.stem.2013.09.015</p> <p><b>Contact:</b> Kim B. Jensen, University of Copenhagen, Copenhagen, Denmark e-mail: <a href="mailto:kim.jensen@bric.ku.dk">kim.jensen@bric.ku.dk</a></p>

**This week in techniques (continued)**

Approach	Summary	Licensing status	Publication and contact information
Immunosuppression regimen to prevent immunotoxin neutralization	A small clinical study suggests combining the immunosuppressive drugs pentostatin and cyclophosphamide could prevent neutralizing antibodies against immunotoxin treatment in cancer. In 11 patients with mesothelioma, combining the 2 drugs with the immunotoxin SS1P, which contains a portion of a bacterial exotoxin, delayed the formation of neutralizing antibodies against the toxin. In 10 evaluable patients, 3 had durable partial responses, 3 had stable disease and 4 had progressive disease. Next steps include planning additional clinical trials.  <i>SciBX</i> 6(46); doi:10.1038/scibx.2013.1336 Published online Dec. 5, 2013	Patent and licensing status undisclosed	Hassan, R. <i>et al. Sci. Transl. Med.</i> ; published online Oct. 23, 2013; doi:10.1126/scitranslmed.3006941 <b>Contact:</b> Raffit Hassan, National Institutes of Health (NIH), Bethesda, Md. e-mail: <a href="mailto:hassanr@mail.nih.gov">hassanr@mail.nih.gov</a>

## Can You Afford Not to Read SciBX?

According to MEDLINE®, the U.S. National Library of Medicine's® premier bibliographic database of articles in life sciences, over 775,000 articles were added to the database in 2009 alone—an average of almost 15,000 new articles every week.

Can you afford to miss investment opportunities?

Can you afford to miss emerging competition?

SciBX is the single source for scientific context, commercial impact and the critical next steps.

Visit [scibx.com](http://scibx.com) for details on how to subscribe to SciBX

**SciBX: Science–Business eXchange**

**Company and institution index**

<b>A</b>	
Altravax Inc.	14
American Chemical Society	4
Antegrin Therapeutics LLC	1,16
AstraZeneca plc	11
<b>B</b>	
Biogen Idec Inc.	3,15
Bristol-Myers Squibb Co.	12
<b>C</b>	
Center for World Health & Medicine at Saint Louis University	3
City of Hope	11
Commonwealth Scientific and Industrial Research Organisation	10
Commonwealth Scientific and Industrial Research Organisation Food and Nutritional Sciences	7
<b>D</b>	
Dynavax Technologies Corp.	11
<b>G</b>	
Genentech Inc.	18
GlaxoSmithKline plc	11
<b>H</b>	
Harvard Medical School	2,8
<b>I</b>	
Icahn School of Medicine at Mount Sinai	2
Immunology Frontier Research Center at Osaka University	8
Institute of Diabetes Research at Helmholtz Center Munich	8
Integral Molecular Inc.	14
International AIDS Vaccine Initiative	14
Isis Pharmaceuticals Inc.	11
<b>K</b>	
Kanazawa University	12
Karolinska Institute	2
Keio University	7
KineMed Inc.	2
<b>L</b>	
Ludwig Center for Cancer Immunotherapy at the Memorial Sloan-Kettering Cancer Center	7
<b>M</b>	
Max Planck Institute for Molecular Biomedicine	2
Melior Discovery Inc.	4
Memorial Sloan-Kettering Cancer Center	10
<b>N</b>	
National Institute of Allergy and Infectious Diseases	2
National Institutes of Health	2,6,16
Novartis AG	12
<b>O</b>	
Otsuka Pharmaceutical Co. Ltd.	11,12

<b>P</b>	
Pfizer Inc.	4
<b>R</b>	
RIKEN	10
RIKEN Center for Integrative Medical Sciences	7
Roche	18
<b>S</b>	
Saint Louis University	2
Saint Louis University School of Medicine	3
<b>T</b>	
Theraclone Sciences Inc.	14
<b>U</b>	
University of California, San Francisco	1,16
University of Edinburgh	2
University of Muenster	2
University of Texas MD Anderson Cancer Center	2
University of Tokyo	7,13
Uppsala University	2
<b>V</b>	
Vernalis plc	13
.....	
<b>Target and compound index</b>	
1,4,7,10-Tetraazacyclododecane-1,4,7,10-Tetraacetic acid	18
3BNC117	15
4-Hydroxy-3-iodophenyl 10-1074	18
<b>A</b>	
$\alpha$ -Sma	2
$\alpha$ -Synuclein	15
Acta2	2
Actin $\alpha$ 2 smooth aorta muscle	2
Adiponectin	13
Adiponectin receptor 1	13
ADIPOQ	13
ADIPOR1	13
ADIPOR2	13
Anandamide	13
Androgen receptor	12
AR	12
Aryloxazole	11
ATGL	13
AZD9150	11
<b>B</b>	
BCR-ABL tyrosine kinase	12
BIIB023	15
Butyrate	7
<b>C</b>	
CCL3	12
CD4	7,15
CD51	1,16
Chlorambucil	11
Cisplatin	18
Class IIa HDAC	7
Constitutive photomorphogenic 1	17
COP1	17
C-ros proto-oncogene 1 receptor tyrosine kinase	18

CWHM 12	2
Cyclophosphamide	19
Cyclosporine	4
<b>D</b>	
Dasatinib	12
DDR1	12
Dengue virus envelope protein E	14
DENV_gp1	14
Derek Nexus	5
Desmolaris	16
Discoidin domain receptor tyrosine kinase 1	12
DNA	11
DOTA	18
DV1179	11
<b>E</b>	
EGFR2	18
Endocannabinoid	13
ErbB2	18
Etoposide	12
<b>F</b>	
FAAH	13
Factor Xa	16
Factor XIa	16
Fatty acid amide hydrolase	13
FIG	18
Forkhead box P3	7,10
FOXP3	7,10
<b>G</b>	
Gleevec	12
Golgi-associated PDZ and coiled-coil motif containing GOPC	18
<b>H</b>	
HDAC	7,10
HER2	18
Herceptin	18
HIP	18
Histone deacetylase	7,10
HIV gp120	14,15
HMG-CoA reductase	17
<b>I</b>	
Imatinib	12
Indolotriazine	17
Integrin	1
Integrin $\alpha_v$	1,16
Integrin $\alpha_v\beta_6$	3
ISIS-STAT3Rx	11
<b>K</b>	
Kallikrein	16
K-Ras	17,18
KRAS	17,18
<b>L</b>	
LKB1	17
Lovastatin	17
<b>M</b>	
Macrophage inflammatory protein-1 $\alpha$	12
MicroRNA-141	10
MIP1A	12
miR-141	10
miR-219	10

<b>N</b>	
NAB	15
NEDD4	15
NEDD4-1	15
NEDD4 family E3 ubiquitin protein ligase	15
Neu	18
Neural precursor cell expressed developmentally downregulated 4	15
Nilotinib	12
N-Arylbenzimidazole	15
<b>O</b>	
OPB-31121	11
<b>P</b>	
Patatin-like phospholipase domain containing 2	13
Pentostatin	19
p53	18
PGT121	14
PNPLA2	13
Propionate	7
<b>R</b>	
Reactive oxygen species	15
REV1	18
REV3L	18
REV3-like catalytic subunit of DNA polymerase- $\zeta$	18
RFWD2	17
ROS	15
ROS1	18
RSP5	15
<b>S</b>	
SCFA	7
Serine/threonine kinase 11	17
Short-chain fatty acid	7,10
Signal transducer and activator of transcription 3	11
SNCA	15
Sprycel	12
SS1P	19
STAT3	11
STK11	17
STX-100	3
Sulfonamide	14
<b>T</b>	
Tasigna	12
TGFB	1
TGFB1	2
TGF $\beta$	1
TLR7	11
TLR9	11
TNF-like weak inducer of apoptosis	15
Toll-like receptor 9	11
Topoisomerase	12
Transforming growth factor- $\beta$	1
Trastuzumab	18
Tubulin	11,14
TWEAK	15
<b>U</b>	
UDP glucuronosyltransferase 2 family polypeptide B15	12
UGT2B15	12
<b>V</b>	
V158866	13