

THIS WEEK

ANALYSIS

COVER STORY

1 Multitasking E selectin

Researchers at the Mater Medical Research Institute, The University of Queensland and GlycoMimetics have mouse data showing that E selectin antagonists can alleviate side effects of chemotherapy brought about by exhaustion of the self-renewal capacity of hematopoietic stem cells. The group is working together to develop E selectin antagonists, but Mater Research and the biotech have different agendas about how to use those antagonists in oncology.

TRANSLATIONAL NOTES

4 Rediscovering antibiotics

The implementation of the Generating Antibiotic Incentives Now (GAIN) Act and other recent efforts to speed antibiotic development will only be successful if they encourage new chemical approaches that address the dearth of new chemical classes in the antibiotics pipeline. Antibiotic developers contacted by *SciBX* said solving bacteria-specific challenges will be addressed only by investing in new structure-guided synthesis and screening programs.

TARGETS & MECHANISMS

7 Solving triptolide

University of Minnesota researchers have developed a water-soluble prodrug of the poorly soluble cancer therapeutic triptolide that could give a second life to the plant-derived compound. Minneamrita Therapeutics holds a license to the new molecule and plans to start a Phase I trial within six months.

9 Sponging out cystic fibrosis

A Canadian team has found that compounds from sea sponges could be useful for treating cystic fibrosis. The compounds work in part by inhibiting a new family of targets for the disease: poly(ADP-ribose) polymerases. The researchers now plan to work backward to uncover why blocking these polymerases improves the function of CFTR, the mutated protein that causes CF.

THE DISTILLERY

11 This week in therapeutics

Treating type 2 diabetes with a GLP-1-estrogen conjugate; and more ...

16 This week in techniques

An assay for viral resistance using binding competition; and more ...

INDEXES

19 Company and institution index**19 Target and compound index**

Multitasking E selectin

By Tracey Baas, Senior Editor

In patients with cancer, repeated rounds of chemotherapy exhaust the self-renewal capacity of hematopoietic stem cells, leading to prolonged bone marrow suppression, cytopenia and neutropenia. Now, researchers at the **Mater Medical Research Institute, The University of Queensland** and **GlycoMimetics Inc.** have mouse data showing that an antagonist of E selectin can alleviate this side effect of chemotherapy.¹

Based on the findings, the team will continue to work together to develop E selectin antagonists, but Mater Research and the biotech are driving different agendas on how to use those antagonists in oncology.

E selectin (SELE; CD62E) belongs to a family of proteins involved in leukocyte homing. Within that family, SELE and SELP (CD62P) are expressed constitutively on the bone marrow endothelium, as well as on endothelial cells from other tissues during injury or inflammation. Both proteins are involved in the homing and engraftment of circulating hematopoietic stem cells (HSCs) and hematopoietic progenitor cells to the bone marrow.

Previous studies showed that quiescent HSCs were enriched near osteoblasts lining the endosteal bone surface and in poorly perfused areas of the bone marrow, leading to the hypothesis that osteoblast factors maintain HSC dormancy and self-renewal.

Because *SELE* also is expressed within the vascular HSC niche adjacent to bone marrow, the researchers set out to determine whether the protein might also play a role in HSC turnover.

To test that hypothesis, the researchers first worked with *Sele* knock-out mice. HSC turnover in those animals was lower than that in wild-type mice, with increased quiescence of HSCs and a greater potential for self-renewal.

Additional studies showed that HSC quiescence was mediated by the bone marrow microenvironment.

Because *Sele* deficiency induced quiescence and self-renewal of HSCs, the researchers next investigated whether the HSCs of *Sele*-deficient mice were more resistant to chemotherapy than HSCs of wild-type mice. Indeed, *Sele*-deficient mice receiving cyclophosphamide or 5-fluorouracil (5-FU) had greater numbers of HSCs that survived than similarly treated wild-type mice.

The increased survival of the HSCs translated into a survival advantage for the *Sele*-deficient mice. For example, *Sele*-deficient mice receiving 5-FU every 10 days had median survival of at least 140 days versus 58 days for wild-type mice receiving 5-FU.

Finally, the team treated mice with GMI-1070, a small, synthetic

**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.; Joanne Kotz, Ph.D.**Writers:** Chris Cain, Ph.D.; Michael Flanagan; Tim Fulmer, Ph.D.;

Michael J. Haas; Stephen Hansen; Kai-Jye Lou; Lauren Martz;

Lev Osheroovich, Ph.D.; Steve Usdin

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**PUBLISHING****Publisher:** Peter Collins, Ph.D.**Associate Publishers:** Gaspar Taroncher-Oldenburg, Ph.D.; Eric Pierce**Marketing:** Sara Girard; Rosy Rogers**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 5333

Chadds Ford

223 Wilmington-West Chester Pike

Chadds Ford, PA 19317

T: +1 610 558 1873

Chicago

20 N. Wacker Drive, Suite 1465

Chicago, IL 60606-2902

T: +1 312 755 0798

Oxford

287 Banbury Road

Oxford OX4 7JA

United Kingdom

T: +44 (0)18 6551 2184

Washington, 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 9200

London

The Macmillan Building

4 Crinan Street

London N1 9XW

United Kingdom

T: +44 (0)20 7833 4000

Tokyo

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 © 2012 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.

glycomimetic that selectively blocks binding of selectins to their receptors. GlycoMimetics and partner **Pfizer Inc.** have the molecule in Phase II testing to treat sickle cell disease.

In wild-type mice undergoing serial bone marrow transplantations to rapidly age HSCs, GMI-1070 increased the self-renewal capacity of HSCs compared with saline. Pretreatment with GMI-1070 followed by 5-FU increased HSC survival and self-renewal compared with pretreatment using 5-FU alone and accelerated blood leukocyte recovery.

Results were published in *Nature Medicine*.

A different *Nature Medicine* study published one month later also revealed repurposing opportunities using an antidiabetic drug (see **Box 1**, “More repurpose”).

Selectin what's next

“Our work identifies one of the master switches regulating the choice a hematopoietic stem cell makes between quiescence and proliferation. We show that by manipulating the microenvironment around a stem cell, we can alter that cell’s response to therapy, its proliferation and self-renewal,” said Ingrid Winkler, team leader at Mater Medical Research Institute.

She said Mater Research is working with **UniQuest Pty. Ltd.**, the University of Queensland’s commercialization arm, and looking toward clinical trials of E selectin inhibitors to treat the side effects of chemotherapy- and radiotherapy-induced disorders, such as neutropenia.

Meanwhile, GlycoMimetics plans to use its small molecule E selectin antagonists to increase the efficacy of chemotherapeutics in blood cancers.

“E selectin is also known to bind and sequester cancer cells—particularly blood cancers—within bone marrow. This is a problem because once dosing with chemotherapy ends, leukemic cells can emerge

SciBX: Science–Business eXchange

*SciBX welcomes editorial queries,
comments and press releases.*

To contact the editorial team at SciBX
please e-mail editorial@scibx.com

Box 1. More repurpose.

An **Indiana University School of Medicine** team has shown that the diabetes drug Januvia sitagliptin can enhance the recovery of hematopoietic stem and progenitor cells after chemotherapy or radiotherapy.² The group is now working out the timing and dosing of the dipeptidyl peptidase-4 (DPP-4) inhibitor in the new indication.

A number of proteins involved in hematopoiesis have DPP-4 truncation sites, which are sites that are cleaved by the peptidase. Previous studies by the Indiana team showed that DPP-4 inhibition can block this truncation and improve a protein's activities. Thus, they wanted to see whether genetic or pharmacological disruptions of DPP-4 would enhance recovery of hematopoietic stem cells (HSCs) after radiation or chemotherapy.

Indeed, *Dpp-4* knockout mice receiving chemotherapy or radiotherapy showed greater hematopoietic progenitor cell (HPC) recovery than wild-type mice receiving the same treatments. In wild-type mice receiving radiation or chemotherapy, pretreatment with Januvia increased HPC and HSC recovery in bone marrow compared with vehicle pretreatment.

Results were published in *Nature Medicine*.

Merck & Co. Inc. and **Ono Pharmaceutical Co. Ltd.** market Januvia to treat type 2 diabetes.

“Our immediate ongoing efforts are focused on identifying the best timing and dosing of sitagliptin and other DPP-4 inhibitors in mice to enhance recovery of neutrophils and platelets after radiation, chemotherapy or stem cell transplantation,” said Hal Broxmeyer, lead author

and professor of microbiology and immunology at the Indiana University School of Medicine.

His lab's overarching efforts are focused on DPP-4 truncation. “A number of biological molecules active on many different cells, tissues and organs have putative DPP-4 truncation sites,” he said. “Our team wants to understand the potential implications of what the truncated molecules may do and what DPP-4 inhibition in these systems may mean. It is our belief that DPP-4 and its inhibition will have far-reaching implications to biology in general, not just for hematopoiesis.”

The university has filed for patents covering the use of DPP-4 inhibitors to improve recovery of neutrophils and platelets after radiation, chemotherapy or stem cell transplantation. The findings are not licensed. —TB

from the bone marrow and result in a relapse,” said John Magnani, VP and CSO of GlycoMimetics. “But we and our collaborators at the **Dana-Farber Cancer Institute** and **Harvard Medical School** showed that GMI-1070 plus Velcade prevents cancer cells from sequestering within protective niches in the bone marrow, thereby increasing the efficacy of the chemotherapy treatment in a mouse model of multiple myeloma.”

Velcade bortezomib is marketed by **Takeda Pharmaceutical Co. Ltd.** and partner **Johnson & Johnson** to treat mantle cell lymphoma and multiple myeloma.

The company said it is testing E selectin-specific antagonists in combination with chemotherapy in mouse models of multiple myeloma (MM), acute myeloid leukemia (AML) and acute lymphocytic leukemia (ALL).

“Our ultimate goal is to treat certain blood cancers with an orally bioavailable, potent E selectin-specific antagonist in combination with standard-of-care chemotherapy,” Magnani said. “We have now rationally designed more potent glycomimetic antagonists that specifically inhibit only E selectin and are optimizing them for oral bioavailability.”

GMI-1070 inhibits E selectin but has activity on other members of the family.

GlycoMimetics holds patents covering GMI-1070 and related pan-selectin antagonists and other families of E selectin-specific antagonists.

“Our ultimate goal is to treat certain blood cancers with an orally bioavailable potent E selectin-specific antagonist in combination with standard-of-care chemotherapy.”

—John Magnani,
GlycoMimetics Inc.

Mater Research holds patents addressing the use of E selectin antagonists to alleviate the side effects, such as neutropenia, that result from radiotherapy or high-dose chemotherapy. The technology is available for licensing through UniQuest.

Baas, T. *SciBX* 5(46); doi:10.1038/scibx.2012.1197
Published online Nov. 29, 2012

REFERENCES

1. Winkler, I.G. *et al. Nat. Med.*; published online Oct. 21, 2012; doi:10.1038/nm.2969
Contact: Jean-Pierre Lévesque, Mater Medical Research Institute, South Brisbane, Queensland, Australia
e-mail: jplevesque@mmri.mater.org.au
Contact: Ingrid G. Winkler, same affiliation as above
e-mail: iwinkler@mmri.mater.org.au
2. Broxmeyer, H.E. *et al. Nat. Med.*; published online Nov. 18, 2012; doi:10.1038/nm.2991
Contact: Hal E. Broxmeyer, Indiana University School of Medicine, Indianapolis, Ind.
e-mail: hbroxmey@iupui.edu

COMPANIES AND INSTITUTIONS MENTIONED

Dana-Farber Cancer Institute, Boston, Mass.
GlycoMimetics Inc., Gaithersburg, Md.
Harvard Medical School, Boston, Mass.
Indiana University School of Medicine, Indianapolis, Ind.
Johnson & Johnson (NYSE:JNJ), New Brunswick, N.J.
Mater Medical Research Institute, South Brisbane, Queensland, Australia
Merck & Co. Inc. (NYSE:MRK), Whitehouse Station, N.J.
Ono Pharmaceutical Co. Ltd. (Tokyo:4528; Osaka:4528), Osaka, Japan
Pfizer Inc. (NYSE:PFE), New York, N.Y.
Takeda Pharmaceutical Co. Ltd. (Tokyo:4502), Osaka, Japan
UniQuest Pty. Ltd., Brisbane, Queensland, Australia
The University of Queensland, Brisbane, Queensland, Australia

Rediscovering antibiotics

By Chris Cain, Senior Writer

The implementation of the Generating Antibiotic Incentives Now Act and other recent efforts to speed antibiotic development will only be successful if they encourage new chemical approaches that address the dearth of new chemical classes in the antibiotics pipeline. Antibiotic developers contacted by *SciBX* said solving bacteria-specific challenges including rapidly emerging resistance and highly active drug export will be addressed only by investing in new structure-guided synthesis and screening programs.

Increased regulatory scrutiny by the FDA and a lack of clear financial motivation have taken their toll on the development of new antibiotics, with a trend of decreasing approvals over the past 30 years¹ (see Figure 1, “Antibiotic approvals over the last three decades in five-year increments”).

Moreover, just two new classes of broad-spectrum antibiotics have been approved in the last 40 years—the oxazolidinone Zyvox linezolid from **Pfizer Inc.** and the lipopeptide Cubicin daptomycin from **Cubist Pharmaceuticals Inc.**—both of which are only effective against Gram-positive bacteria. And reports of emerging multidrug-resistant Gram-negative bacteria, such as *Acinetobacter*, have stoked further concerns that there is not a robust pipeline of drugs to deal with the multiplicity of threats posed by an overall highly diverse and variable spectrum of pathogenic bacteria.

Jeffrey Stein, president and CEO of **Trius Therapeutics Inc.**, told *SciBX* that when it comes to antibiotic development, it has been a lack of financial incentives, and not scientific hurdles, that has stymied work. “The biggest challenge is not technical, it is financial, and that is because there is very little investment or interest in the early stage research required to come up with a clinical compound.”

To encourage companies to invest in antibiotics, the U.S. Congress passed the Generating Antibiotic Incentives Now (GAIN) Act, which took effect Oct. 1 as part of the FDA Safety and Innovation Act, which reauthorized prescription drug user fees. The law provides automatic priority review and an additional five to seven years of market exclusivity for some qualified infectious disease products (QIDPs).²

Members of Congress and biotech executives discussed how the legislation could aid antibiotic development on “*BioCentury This Week*” earlier this month. FDA officials also discussed the agency’s Antibacterial Drug Development Task Force on a second “*BioCentury This Week*” program devoted to the topic.

Although the impact of the GAIN Act will take time to measure, several biopharma executives said it represents a sea change in attitudes toward antibiotic development.

Mark Leuchtenberger, president and CEO of **Rib-X Pharmaceuticals Inc.**, told *SciBX*, “The overall environment has turned from its nadir in the late 2000s, when four drugs went in front of FDA and only one

came out. With initiatives in Europe and support from BARDA, there is now a much more propitious environment than there has been since the late ‘90s.”

The **Biomedical Advanced Research and Development Authority** (BARDA) is a U.S. Department of Health and Human Services program that prepares for potential public health emergencies in part by funding the development and purchase of drugs and vaccines.

In September, Rib-X’s lead compound, delafloxacin, was granted the first publically announced QIDP designation. The company plans to begin Phase III testing of the fluoroquinolone for acute bacterial skin and skin structure infections (ABSSSI) by the end of 2Q13.

John Rex, VP and head of infection and global medicines development at **AstraZeneca plc**, agreed with Leuchtenberger. “The whole tone of the conversation has gone from ‘no’ to ‘go,’” he said in an interview this month with *BioCentury*.²

Indeed, the EU’s **Innovative Medicines Initiative** (IMI) recently announced a €223.7 million (\$281.6 million) effort called New Drugs for Bad Bugs (ND4BB) to fund the clinical development of new antibiotics and create a consortium dedicated to basic research into Gram-negative pathogens.³

Until these efforts were proposed and implemented over the past year, “the incentives weren’t there from an early stage investor perspective,” said Ankit Mahadevia, a principal in the life sciences group at **Atlas Venture**. “Now we see the evolution of the landscape to be a lot like how the orphan drug landscape evolved several years ago. If there is pricing support for premium-priced antibiotics, there is a reasonable investment thesis

“The biggest challenge is not technical, it is financial, and that is because there is very little investment or interest in the early stage research required to come up with a clinical compound.”

—Jeffrey Stein,
Trius Therapeutics Inc.

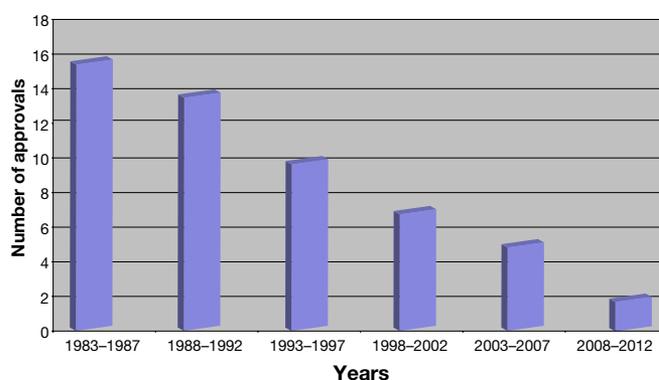


Figure 1. Antibiotic approvals over the last three decades in five-year increments. In 1983–1987 the FDA approved 16 new systemic antibiotics, but since that time antibiotic approvals have been on the decline. Since 2008, only two systemic antibiotics have been approved. Vibativ telavancin from **Theravance Inc.** was approved in 2009 to treat acute bacterial skin and skin structure infections (ABSSSI), and Teflaro ceftaroline from **Forest Laboratories Inc.** was approved in 2010 to treat community-acquired bacterial pneumonia (CABP) and ABSSSI. (Figure based on Figure 1 in ref. 1.)

Source: Spellberg et al.; *BCIQ: BioCentury Online Intelligence*

around investing early, and as time goes on pharma will come back into the fold.”

The challenge now is to channel the optimism into new chemical classes of broad-spectrum antibiotics. The existing [clinical pipeline](#) is sorely lacking novelty, with no new classes of compounds in Phase III testing and only two in Phase II development.

Structural challenges

Companies leading the charge to develop new classes of antibiotics told *SciBX* that reliance on past approaches is not enough to fill the pipeline. Instead, recent structural and chemical advances must guide the discovery of the next generation of antibiotics.

Rib-X CSO Erin Duffy said the low rate of new antibiotic development is caused in part by not using the right kind of starting chemical matter in enzymatic or cell-based screens. “The approach of saying, ‘I want to hit target X; I’ll screen until I get something’ didn’t work well because corporate libraries aren’t full of antibiotic-like compounds,” she said.

Stein agreed. “High throughput screening against large libraries has been largely ineffective. Most existing libraries and medicinal chemists who try to design new compounds create very lipophilic compounds. This means the solubility is very poor, and they do not cross bacterial membranes very well,” he said.

“The other truth is that people are pretty risk adverse. Everyone loves the idea of a novel scaffold, but they also hate the idea because they aren’t going to know what they get,” Duffy added.

Both Trius and Rib-X are taking a structure-based approach to design new antibiotics.

Rib-X is focused on antibiotics targeting the ribosome. The company has two new antibacterial programs in preclinical development, one of which is partnered with **Sanofi**.

Trius is developing new antibiotics against a range of bacterial targets including topoisomerase IV, DNA gyrase and the bacterial cell-wall enzyme UDP-N-acetylenolpyruvylglucosamine reductase (murB).

Stein said that innovation in the space is mostly coming from within biotech. “The truly novel antibacterials are being developed in small companies. Academic labs don’t have the funding to do this, and in large companies, those few that are doing antibacterial research are working on the next-generation cephalosporins or carbapenems. There is a limitation to how many generations you can make.”

However, Manos Perros, head of AstraZeneca’s Infection Innovative Medicines Unit (iMed), pointed out that his group also is investing in new chemical approaches. “My sense is there have been developments in the last three to four years that we can take advantage of, advances in chemistry for one, as illustrated by our collaboration with the Broad Institute, where we can generate chemical starting points that look more like natural-product antibiotics, and thus we can start programs from a better place,” he said.

Last September, the pharma partnered with the **Broad Institute of MIT and Harvard** to screen a library of 100,000 compounds made by diversity-oriented synthesis, a process that generates molecular structures not contained in standard compound collections.

Cempra Inc. founder, president and CEO Prabhavathi Fernandes said it is important that new synthetic compounds interact with multiple sites on a target, as is the case for many naturally derived antibiotics. “When compounds inhibit a single site you get mutations and resistance

develops. That is why natural products have been so popular—they bind multiple sites, and if bacteria mutate each site they either die or they are too sick to grow.”

Tetraphase Pharmaceuticals Inc. SVP of biology Joyce Sutcliffe agreed and emphasized that there is still room for new natural product-inspired antibiotics to overcome existing resistance mechanisms. “Knowing what the devil is often gives you an advantage,” she said.

Tetraphase is using its synthetic chemistry platform to develop new derivatives of tetracycline, a broad-spectrum polyketide antibiotic with activity against Gram-positive and Gram-negative bacteria. The company’s lead program, Eravacycline, has completed Phase II testing in community-acquired complicated intra-abdominal infections (cIAIs).

Both Sutcliffe and Fernandes pointed to the suspension earlier this year of clinical trials of GSK2251052, a bacterial leucyl-tRNA synthetase (lars; leurs) inhibitor from **GlaxoSmithKline plc** and **Anacor Pharmaceuticals Inc.**, as an example of how resistance can derail an antibiotic program focused on a single new target.

GSK returned rights to the compound to Anacor last month after resistance developed in a Phase IIb trial to treat urinary tract infection (UTI).

GSK still has two new broad-spectrum agents in the clinic. GSK1322322, a bacterial peptide deformylase (pdf) inhibitor, has completed Phase II testing and will enter Phase III trials as part of IMI’s ND4BB program. GSK2140944, a new bacterial topoisomerase IIA inhibitor, is in Phase I development.⁴

Cempra’s lead program is solithromycin, a fluoroketolide antibiotic that interacts with multiple sites on bacterial 23S rRNA. The compound is slated to begin Phase III testing to treat community-acquired bacterial pneumonia (CABP) Q412.

Gram negativity

The need for new chemical matter is particularly urgent for Gram-negative bacterial infections, which present unique challenges to the development of new drug classes.

“In terms of getting to a Gram-negative [bacteria] there are a lot more things at play. They have two membranes—and the outer membrane is pretty impermeable. If you can get through that and on your way to a molecular target, then you have to be able to test efflux, which is a problem in Gram positives but is really an issue in Gram negatives, which have 40 different efflux pumps. You have to figure out how not to be a substrate for that,” said Duffy.

To better understand these efflux pumps, ND4BB is spending €24 million (\$30 million) on new *in vitro* assays to study penetration and efflux in multidrug-resistant Gram-negative bacteria, on bacterial porin structure and function research, on studies of nutrient uptake systems to identify new points of entry for antibiotics and on genetic screens to identify previously unknown targets that could improve drug penetration or reduce efflux.

“This is a place where the academic community could put their muscle to work,” said Sutcliffe.

AstraZeneca, **Basilea Pharmaceutica AG**, GSK, the Janssen R&D unit of **Johnson & Johnson** and Sanofi are participating in the effort.

Despite the challenges, Mahadevia said he was most interested in programs focused on Gram-negative bacteria. “Generally, I think Gram positives are well served by the pipeline and existing products. Gram negatives are where we are looking, pan-Gram-negative agents, but also

targeting specific bugs such as *Pseudomonas*.”

Cempra’s Fernandes said it is important to keep historical perspective and not focus too narrowly on Gram-negative bacteria. “The unfortunate thing is we don’t know where the next bad bug is going to come from. Let’s say it is *Acinetobacter* now, but tomorrow it could be β -*Streptococcus*. We will need drugs against every major class of pathogens, and we cannot focus only on Gram negatives. Ten years ago all the focus was on staph, and no one looked at Gram negatives. Now it is all on Gram negatives.”

Future gazing

The development of rapid diagnostic tests to guide the clinical use of antibiotics also is a key next step to encourage antibiotic development. Identifying the causative agent of an infection is still a slow process relative to the lifetime of the infection; thus, antibiotic efficacy and approval rates would benefit from such improved detection methodologies.

Fernandes said designing a drug that treats a specific indication, rather than a specific pathogen, adds to the development challenge facing antibiotics. “When you talk about an infection, it’s not one disease. Let’s take pneumonia for example. There are five, six, seven bacteria that could cause the disease, and you have to treat all five bacteria with the same drug. There are many different targets there that you have to kill,” she said.

Cempra is collaborating with **Curetis AG** to use Curetis’ rapid diagnosis platform to collect data in Cempra’s Phase III CABP trial of solithromycin.

Rib-X’s Leuchtenberger also said that molecular diagnostics are promising but development is difficult. “All the key opinion leaders have said an accurate diagnostic is just around the corner for years, and it’s not there yet.”

AstraZeneca’s Perros agreed that the development of diagnostics for infectious diseases is an area in which more work is needed. “The way we treat disease today is empirical—every hour that passes reduces a patient’s chance for survival if you use the wrong antibiotics, so if you are in doubt you use the one with the broadest coverage and with activity against resistant infections. If you have a diagnostic that could easily tell you whether the patient needs the new drug, it would achieve several things in one—you would not treat patients with a new drug you don’t need and unnecessarily drive up treatment cost, and you would avoid promoting unnecessary development of resistance to our latest treatments,” he said.

“I think Gram positives are well served by the pipeline and existing products. Gram negatives are where we are looking.”

—Ankit Mahadevia, Atlas Venture

Perros said AstraZeneca is working in this area but has not disclosed specific antibacterial diagnostic partnerships.

Stein said molecular diagnostics could be particularly important for late-stage development. “It would be meaningful in a Phase III trial. For example, for a Gram-positive spectrum drug such as tedizolid, if it’s a lung study where

Gram-negative or Gram-positive [bacterial] could be involved, it’s going to be important to prescreen prior to enrollment,” he said.

Trius’ tedizolid is in Phase III development for ABSSSI.

Sutcliffe agreed that for certain indications, such as CABP, a diagnostic could help reduce trial size and cost. However, she pointed out that it can be difficult to develop a specific antibacterial diagnostic to pinpoint the cause of an infection. “This is much harder than the diagnostics for antivirals because there aren’t usually intrinsic viruses running around in your blood stream. In the intestinal tract there are thousands of species of bacteria; if you take a sample there how will you know for sure which one is the causative pathogen?”

Cain, C. *SciBX* 5(46); doi:10.1038/scibx.2012.1198
Published online Nov. 29, 2012

REFERENCES

1. Spellberg, B. *et al. Clin. Infect. Dis.* **46**, 155–164 (2008)
2. Usdin, S. *BioCentury* **20**(47), A1–A7; Nov. 19, 2012
3. Cain, C. *BioCentury* **20**(23), A1–A4; June 4, 2012
4. Lou, K.-J. *SciBX* **3**(34); doi:10.1038/scibx.2010.1031

COMPANIES AND INSTITUTIONS MENTIONED

Anacor Pharmaceuticals Inc. (NASDAQ:ANAC), Palo Alto, Calif.

AstraZeneca plc (LSE:AZN; NYSE:AZN), London, U.K.

Atlas Venture, Cambridge, Mass.

Basilea Pharmaceutica AG (SIX:BSLN), Basel, Switzerland

Biomedical Advanced Research and Development Authority, Washington, D.C.

Broad Institute of MIT and Harvard, Cambridge, Mass.

Cempra Inc. (NASDAQ:CEMP), Chapel Hill, N.C.

Cubist Pharmaceuticals Inc., (NASDAQ:CBST), Lexington, Mass.

Curetis AG, Holzgerlingen, Germany

Food and Drug Administration, Silver Spring, Md.

GlaxoSmithKline plc (LSE:GSK; NYSE:GSK), London, U.K.

Innovative Medicines Initiative, Brussels, Belgium

Johnson & Johnson (NYSE:JNJ), New Brunswick, N.J.

Pfizer Inc. (NYSE:PFE), New York, N.Y.

Rib-X Pharmaceuticals Inc., New Haven, Conn.

Sanofi (Euronext:SAN; NYSE:SNY), Paris, France

Tetraphase Pharmaceuticals Inc., Watertown, Mass.

Trius Therapeutics Inc. (NASDAQ:TSRX), San Diego, Calif.

Solving triptolide

By Kai-Jye Lou, Staff Writer

University of Minnesota researchers have developed a water-soluble prodrug of the poorly soluble cancer therapeutic triptolide that could give a second life to the plant-derived compound.¹ **Minneamrita Therapeutics LLC** holds a license to the new molecule and plans to start a Phase I trial within six months.

Triptolide is a diterpenoid triepoxide derived from the traditional Chinese medicine plant *Tripterygium wilfordii*.

In early 2007, researchers at the University of Minnesota led by Ashok Saluja showed that small interfering RNA-mediated knockdown of heat shock protein 70 (Hsp70) potentially killed pancreatic cancer cells,² which prompted them to search for pharmacological agents that inhibit the protein.

Later that year, Saluja and colleagues showed that triptolide potentially killed pancreatic cancer cells by downregulating Hsp70.³ However, after working with the compound and showing antiproliferative effects in two other forms of cancer,^{4,5} it became clear that triptolide was not suited for clinical development.

“Triptolide is not very soluble in water, so if we were to try to deliver it to a patient we would first need to dissolve it in solvents, which could be very harsh to the patient,” said Saluja, professor and vice chair of research in the Department of Surgery at the University of Minnesota and a cofounder of Minneamrita. “Thus, we decided to modify the compound to make it more water soluble.”

The resulting compound, called minnelide, is designed to release the parent molecule when exposed to phosphatases (see Figure 1, “Model of triptolide release from minnelide”).

An *in vitro* bioconversion assay showed that minnelide had a half-life of about two minutes in the presence of alkaline phosphatase and was rapidly converted into triptolide. In five human pancreatic cancer cell lines, minnelide in the presence of alkaline phosphatase significantly decreased cell viability at nanomolar concentrations compared with no treatment ($p < 0.05$).

In transgenic and xenograft mouse models of pancreatic cancer, intraperitoneal injection of minnelide caused tumor regression and led to a 90% survival rate, whereas saline-treated controls had a 10% survival rate. In one of the mouse xenograft models, minnelide caused more potent reductions in tumor burden than Gemzar gemcitabine, which is marketed by **Eli Lilly and Co.** for pancreatic cancer.

No supplementation of alkaline phosphatase was needed in the mouse studies as the enzyme already is present in blood and many bodily tissues.

Results were published in *Science Translational Medicine*.

“The data in our current study show that minnelide is very effective for treating pancreatic cancer,” said Saluja, corresponding author of the paper. “We showed in multiple types of mouse pancreatic cancer models that treatment with minnelide causes the tumors to quickly melt away.”

“Triptolide was an attractive starting point for synthesizing analogs because the molecule had proven anticancer and antiangiogenic

properties,” added Gunda Georg, coauthor of the paper, professor and department head of medicinal chemistry at the University of Minnesota and director of the university’s Institute for Therapeutics Discovery and Development. “There was also evidence in the literature to suggest that the compound acts via a mechanism of action that is distinct from that of existing chemotherapy drugs and also could potentiate the effect of other chemotherapy agents.”

Indeed, data published by a research group in Europe in 2009 showed that triptolide had a unique antiproliferative profile against the NCI-60 panel of tumor cell lines.⁶

Despite the observed downregulation of Hsp70 activity, Saluja noted that the exact molecular target of triptolide—and thus minnelide—remains unclear.

“We previously found that triptolide inhibited Hsp70 and thought that this was its primary mechanism of action, but we now know that the compound can also inhibit multiple other cancer-associated pathways, such as NF- κ B and other antiapoptosis pathways,” he told *SciBX*.

A working prodrug strategy

There have been multiple past efforts to develop triptolide prodrugs to treat cancer, but none has panned out.

Georg gave the example of F60008, a prodrug developed by a group at **Erasmus Medical Center** that uses a succinate-based prodrug approach. The conversion of F60008 into triptolide was unpredictable and incomplete, and the researchers discontinued development of the prodrug after two reports of death in an investigator-led Phase I dose-escalation study in patients with advanced solid tumors.⁷

Minneamrita expects that the rapid and consistent pharmacokinetics behind minnelide’s conversion into triptolide could give it an edge over previous attempts.

According to Georg, steric hindrance caused by the prodrug group being in close proximity to the active molecule may have contributed to F60008’s unpredictable and incomplete conversion into triptolide.

“With minnelide, the cleavage site for the prodrug group is further out from the active molecule, so we would expect less steric hindrance and thus faster and more complete conversion of the compound into triptolide,” she told *SciBX*.

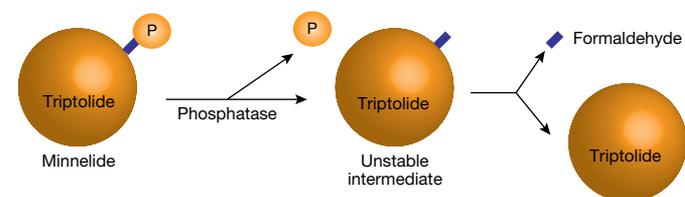


Figure 1. Model of triptolide release from minnelide. Minnelide consists of a phosphonoxyethyl prodrug group that increases the compound’s solubility in water.

Phosphatases, which are present in blood and many bodily tissues, cleave the phosphate group from minnelide to yield an unstable O-hydroxymethyl intermediate. This intermediate then degrades into formaldehyde and the anticancer compound triptolide.

Georg added that a prodrug that releases its drug reliably would allow for much better control over drug levels and toxicity than one with unpredictable release.

Saluja said Minneamrita plans to start recruiting patients in a Phase I trial of minnelide within six months. He said the company wants to position minnelide as a monotherapy to treat patients with pancreatic cancer for whom Gemzar has failed.

In parallel, Saluja said his group at the university is running preclinical studies to determine the potential of using minnelide in combination with Gemzar or inhibitors of tumor necrosis factor–related apoptosis-inducing ligand (TRAIL) in pancreatic cancer. His group also is trying to determine what other cancers could be treated with minnelide and to elucidate the mechanisms underlying the compound's effects.

The University of Minnesota has filed a patent covering triptolide prodrugs including minnelide. The IP is licensed to Minneamrita.

Lou, K.-J. *SciBX* 5(46); doi:10.1038/scibx.2012.1199

Published online Nov. 26, 2012

REFERENCES

1. Chugh, R. *et al. Sci. Transl. Med.*; published online Oct. 17, 2012; doi:10.1126/scitranslmed.3004334
Contact: Ashok K. Saluja, University of Minnesota, Minneapolis, Minn. e-mail: asaluja@umn.edu
2. Aghdassi, A. *et al. Cancer Res.* **67**, 616–625 (2007)
3. Phillips, P.A. *et al. Cancer Res.* **67**, 9407–9416 (2007)
4. Antonoff, M.B. *et al. Surgery* **146**, 282–290 (2009)
5. Clawson, K.A. *et al. J. Surg. Res.* **163**, 244–249 (2010)
6. Vispé, S. *et al. Mol. Cancer Ther.* **8**, 2780–2790 (2009)
7. Kitzen, J.J.E.M. *et al. Eur. J. Cancer* **45**, 1764–1772 (2009)

COMPANIES AND INSTITUTIONS MENTIONED

Eli Lilly and Co. (NYSE:LLY), Indianapolis, Ind.

Erasmus Medical Center, Rotterdam, the Netherlands

Minneamrita Therapeutics LLC, Moline, Ill.

University of Minnesota, Minneapolis, Minn.

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 for details on how to subscribe to SciBX

SciBX: Science–Business eXchange

Sponging out cystic fibrosis

By Lev Osherovich, Senior Writer

A Canadian team has found that compounds from sea sponges could be useful for treating cystic fibrosis. The compounds work in part by inhibiting a new family of targets for the disease: poly(ADP-ribose) polymerases.¹ The researchers now plan to work backward to uncover why blocking these polymerases improves the function of cystic fibrosis transmembrane conductance regulator, the mutated protein that causes cystic fibrosis.

CF results from loss-of-function mutations in cystic fibrosis transmembrane conductance regulator (CFTR), an ion channel that helps lubricate the epithelial lining of lungs, pancreas and intestine. Patients who inherit two mutated copies of *CFTR* develop thick mucus and are prone to severe respiratory infections and digestive problems.

The most common CF-associated CFTR mutation, $\Delta F508$, is a genetic deletion of a single amino acid within the protein. Whereas wild-type CFTR functions on the cell surface, the $\Delta F508$ protein is flagged as defective by cellular quality control mechanisms and becomes trapped in the endoplasmic reticulum (ER).

Notably, the $\Delta F508$ version of CFTR can still function as an ion channel if it can make it to the cell surface. Thus, one therapeutic strategy has been to find compounds that change the ER's metabolism to allow the mutant CFTR to proceed to the cell surface.

An alternative strategy, pursued by **Vertex Pharmaceuticals Inc.**, is to hit mutant CFTR directly with molecules that fix its structure, allowing the defective protein to pass muster with the ER quality control system.

Since 2001, a team led by David Thomas, chair of the Department of Biochemistry at **McGill University**, also has run screens in collaboration with **GlaxoSmithKline plc** to find small molecules that improve cell surface expression of CFTR.

Now, the McGill team has reported on two new hits coming out of those screens—latonduine A and latonduine B (ethyl). The two closely related compounds originally were isolated from the sea sponge *Stylissa carteri*.

“Most of the molecules found so far have been either direct structural modulators of CFTR or metabolic regulators of ER quality control,” said postdoctoral research associate Graeme Carlile, the team's coleader. “This molecule, latonduine, falls into the latter category.”

GSK researchers were not authors on the paper, and the company declined to comment on the work.

Under the C

Carlile and Thomas screened a library of 720 compounds from marine organisms and found that latonduine A and latonduine B (ethyl) increased the surface expression of transgenic $\Delta F508$ CFTR in hamster cells compared with vehicle.

The increase in cell surface expression of $\Delta F508$ CFTR allowed

the protein to do its job of transporting chloride ions out of the cell. Latonduine A-treated lung epithelium cells from patients with CF had about half the ion secretion of cells expressing wild-type CFTR, whereas untreated cells had nearly zero ion secretion. Likewise, mice with the $\Delta F508$ Cfr mutation had higher levels of salivary secretion after latonduine A treatment than untreated controls. Because latonduine A was the better compound, it was used in subsequent experiments.

As latonduines did not appear to directly bind CFTR, Carlile and Thomas made a radiolabelled derivative of latonduine and used it to pull down a family of proteins that bound to it *in vitro*.

Those proteins all turned out to be members of the poly(ADP-ribose) polymerase (PARP) family. PARPs add the post-translational modifier poly(ADP-ribose) to a variety of proteins that regulate many basic cell processes.

More than a dozen PARPs have been identified in humans, and several have been implicated in cancer. At least three PARP inhibitors are in Phase II testing for cancer: olaparib (AZD2281) from **AstraZeneca plc**, veliparib (ABT-888) from **Abbott Laboratories** and rucaparib (CO-338) from partners **Clovis Oncology Inc.**, **Pfizer Inc.** and **Cancer Research**

UK. The anticancer effects of those molecules are thought to result primarily from inhibition of PARP-1 and PARP-2.

In contrast, Carlile and Thomas found that latonduines *in vitro* inhibited another family member, PARP-3, more potently than other PARPs. Moreover, partial knockdown of *PARP-3* but not other *PARPs* enhanced the effect of latonduine A on $\Delta F508$ CFTR surface expression in cell culture.

Although *PARP-3* knockdown made CF cells more sensitive to latonduine A, knocking down the gene in the absence of the drug did not by

itself improve $\Delta F508$ CFTR. This suggests there are other targets besides PARP-3 that contribute to the compound's effect.

Carlile suspects latonduine may act by inhibiting other PARPs in addition to PARP-3. He said one likely suspect could be PARP-16. In October, **Massachusetts Institute of Technology** researchers reported that PARP-16 resides in the ER and participates in the unfolded protein response, putting it in the right place to potentially play a role in CFTR trafficking.²

Results were reported in *Chemistry & Biology*.

PARP for the course

The question now is why reducing PARP activity has a beneficial effect on $\Delta F508$ CFTR.

“There's not much literature on PARP-3, but what we do know is that it works in the nucleus,” said Carlile. “Prior to this work, we had no evidence of PARP involvement on CFTR metabolism.”

Carlile said that the first-generation latonduines used in his study are most likely not suitable as therapeutics because of their promiscuous binding to multiple PARPs. Thus, he plans to conduct SAR studies to find latonduine derivatives with even higher specificity for PARP-3 over other PARPs.

“I think the significance of the work is not so much about finding a corrector of $\Delta F508$ CFTR dysfunction but rather the identification of

“Most of the molecules found so far have been either direct structural modulators of CFTR or metabolic regulators of ER quality control. This molecule, latonduine, falls into the latter category.”

—Graeme Carlile,
McGill University

a potentially novel target,” said Frederick Van Goor, head of biology in the CF research program at Vertex. “Using this molecule to pull out this target was not necessarily expected.”

Vertex’s VX-809 acts on mutant CFTR and corrects its structure so that it can leave the ER.³ The compound has completed Phase II testing in CF in combination with Kalydeco ivacaftor, a potentiator that enhances CFTR’s ion transport activity.

Vertex markets Kalydeco for patients who carry a different CFTR mutation, G551D, which leads to impaired ion transport by the protein.

“As multiple targets are involved in CFTR processing and trafficking, it remains to be determined if hitting one target in particular, such as PARP-3, would have a sufficient effect,” said Van Goor.

It is possible that latonduine derivatives with higher selectivity for PARP-3 might turn out to be less effective than the original promiscuous compounds. On the other hand, broad-spectrum PARP inhibitors run the risk of safety problems due to knock-on effects on multiple targets.

He suggested that further mechanistic cell culture studies are needed to uncover what happens to $\Delta F508$ CFTR when PARP-3 or other PARPs are inhibited. He also recommended testing latonduine derivatives in other cell culture and animal models that more closely resemble CF than the transgenic cell lines used by the McGill team.

Van Goor also noted that inhibiting PARPs could alter the trafficking of other proteins besides CFTR. Because of the concerns about knock-on effects on other proteins, he said Vertex has focused its screening efforts on compounds that are selective for CFTR.

Carlile said preliminary data suggest inhibiting PARP-3 does not affect the bulk flow of proteins out of the ER, “so there is some hope that this is a specific interaction with CFTR.”

According to Carlile, the composition of matter and therapeutic use of latonduines were previously patented by **The University of British Columbia**. Researchers at that university were coauthors on the current study.

At least two other companies—Pfizer and **Proteostasis Therapeutics Inc.**—are developing small molecule therapeutics specifically for $\Delta F508$ CFTR.

Under a deal announced in November, Pfizer will receive up to \$58 million from **Cystic Fibrosis Foundation Therapeutics Inc.** (CFFT), the drug development affiliate of the **Cystic Fibrosis Foundation**, to develop preclinical candidates for $\Delta F508$ CFTR-associated CF. The co-development deal follows up on a 2007 deal between CFFT and FoldRx Pharmaceuticals Inc., which Pfizer acquired in 2010.

In May, CFFT partnered with Proteostasis to identify small molecule modulators of $\Delta F508$ CFTR folding and function.

Osherovich, L. *SciBX* 5(46); doi:10.1038/scibx.2012.1200
Published online Nov. 29, 2012

REFERENCES

1. Carlile, G.W. *et al. Chem. Biol.*; published online Oct. 26, 2012; doi:10.1016/j.chembiol.2012.08.014
Contact: Graeme W. Carlile, McGill University, Montreal, Quebec, Canada
e-mail: graeme.carlile@mcgill.ca
2. Jwa, M. & Chang, P. *Nat. Cell Biol.* **14**, 1223–1230 (2012)
3. Van Goor, F. *et al. Proc. Natl. Acad. Sci. USA* **108**, 18843–18848 (2011)

COMPANIES AND INSTITUTIONS MENTIONED

Abbott Laboratories (NYSE:ABT), Abbott Park, Ill.
AstraZeneca plc (LSE:AZN; NYSE:AZN), London, U.K.
Cancer Research UK, London, U.K.
Clovis Oncology Inc. (NASDAQ:CLVS), Boulder, Colo.
Cystic Fibrosis Foundation, Bethesda, Md.
Cystic Fibrosis Foundation Therapeutics Inc., Bethesda, Md.
GlaxoSmithKline plc (LSE:GSK; NYSE:GSK), London, U.K.
Massachusetts Institute of Technology, Cambridge, Mass.
McGill University, Montreal, Quebec, Canada
Pfizer Inc. (NYSE:PFE), New York, N.Y.
Proteostasis Therapeutics Inc., Cambridge, Mass.
The University of British Columbia, Vancouver, British Columbia, Canada
Vertex Pharmaceuticals Inc. (NASDAQ:VRTX), Cambridge, Mass.

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

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				
Multiple sclerosis (MS)	Mucosa associated lymphoid tissue lymphoma translocation gene 1 (MALT1)	<i>In vitro</i> and mouse studies suggest inhibiting MALT1 could help treat MS. In mice, knockout of <i>Malt1</i> prevented development of experimental autoimmune encephalomyelitis (EAE) and decreased infiltration of T helper type 17 (Th17) cells into the brain and spinal cord compared with no knockout. In wild-type mice, injection of wild-type, autoreactive Th17 cells induced EAE, whereas injection of autoreactive, <i>Malt1</i> ^{-/-} Th17 cells did not. Next steps could include evaluating MALT1 inhibitors in an animal model of MS. SciBX 5(46); doi:10.1038/scibx.2012.1201 Published online Nov. 29, 2012	Patent and licensing status unavailable	Brüstle, A. <i>et al. J. Clin. Invest.</i> ; published online Nov. 1, 2012; doi:10.1172/JCI63528 Contact: Tak W. Mak, The Campbell Family Cancer Research Institute at The Princess Margaret Cancer Centre, Toronto, Ontario, Canada e-mail: tmak@uhnres.utoronto.ca
Cancer				
Cancer	Aurora kinase B (AURKB; aurora-B)	<i>In vitro</i> and mouse studies identified an AURKB-specific inhibitor that could help treat cancer. In a ligand-docking screen, a specific inhibitor of AURKB was identified that did not act on 49 other kinases, including AURKA (aurora-A). In human lung cancer cells, the inhibitor induced apoptosis and cell-cycle arrest and decreased anchorage-independent cell growth compared with vehicle control. In a mouse xenograft model of human lung cancer, intraperitoneal injection of the inhibitor suppressed tumor growth, whereas vehicle injection did not. Next steps could include additional animal safety studies. At least four companies have inhibitors of the aurora kinases in clinical and preclinical development to treat cancers. SciBX 5(46); doi:10.1038/scibx.2012.1202 Published online Nov. 29, 2012	Patent application filed covering the aurora kinase inhibitors; available for licensing	Xie, H. <i>et al. Cancer Res.</i> ; published online Nov. 1, 2012; doi:10.1158/0008-5472.CAN-12-2784 Contact: Zigang Dong, University of Minnesota, Austin, Minn. e-mail: zgdong@hi.umn.edu
Cancer	IL-15; IL-15 receptor α -chain (IL-15RA); apolipoprotein A-1 (APOA1)	Mouse studies suggest a triple fusion protein of APOA1, IL-15 and IL-15RA's sushi domain could prevent cancer metastasis. In a mouse model of metastatic melanoma or metastatic colorectal cancer, vector-induced expression of the triple fusion protein led to fewer metastatic lesions than vector-induced expression of an APOA1 and IL-15 fusion protein plus the IL-15RA sushi domain. In the mouse model of metastatic melanoma, 50 μ g of the recombinant triple fusion protein decreased lung metastases compared with saline. Ongoing work includes exploring the synergy of the triple fusion protein with other cancer therapeutics. Digna Biotech S.L. has the triple fusion protein in preclinical development. SciBX 5(46); doi:10.1038/scibx.2012.1203 Published online Nov. 29, 2012	Patent applications filed; exclusively licensed to Digna Biotech	Ochoa, M.C. <i>et al. Cancer Res.</i> ; published online Nov. 13, 2012; doi:10.1158/0008-5472.CAN-12-2660 Contact: Ignacio Melero, University of Navarra, Navarra, Spain e-mail: imelero@unav.es

This week in therapeutics (continued)

Indication	Target/marker/ pathway	Summary	Licensing status	Publication and contact information
Cancer	Phosphoglycerate mutase 1 (PGAM1)	<p>Mouse and cell culture studies suggest inhibiting PGAM1 could help treat cancer. In a panel of six human cancer cell lines, small hairpin RNA knockdown of PGAM1 decreased proliferation compared with no knockdown. In a mouse xenograft model of human non-small cell lung cancer (NSCLC), pharmacological inhibition of PGAM1 lowered tumor volume compared with no inhibition. In patient samples, the PGAM1 inhibitor decreased viability of primary acute and chronic myelogenous leukemia cells compared with vehicle. Next steps include additional SAR studies to improve the pharmacokinetics and bioavailability of the PGAM1 inhibitors.</p> <p>SciBX 5(46); doi:10.1038/scibx.2012.1204 Published online Nov. 29, 2012</p>	Patent pending; available for licensing from the Emory University Office of Technology Transfer	<p>Hitosugi, T. <i>et al. Cancer Cell</i>; published online Nov. 13, 2012; doi:10.1016/j.ccr.2012.09.020 Contact: Jing Chen, Emory University School of Medicine, Atlanta, Ga. e-mail: jchen@emory.edu Contact: Chuan He, The University of Chicago, Chicago, Ill. e-mail: chuanhe@uchicago.edu</p>
Prostate cancer	Proprotein convertase subtilisin/kexin type 6 (PCSK6; PACE4)	<p><i>In vitro</i> studies identified a selective PACE4 inhibitor that could help treat prostate cancer. SAR studies identified a peptide sequence that selectively inhibited the cancer-associated PACE4 with more than 20-fold selectivity over furin, a closely related proprotein convertase required by normal tissues. In PACE4-expressing prostate cancer cell lines, the peptide decreased cell proliferation compared with vehicle and induced cell cycle arrest. Next steps include toxicity and pharmacokinetic studies.</p> <p>SciBX 5(46); doi:10.1038/scibx.2012.1205 Published online Nov. 29, 2012</p>	Patent applications filed; undisclosed partner has option to license technology; unavailable for licensing	<p>Levesque, C. <i>et al. J. Med. Chem.</i>; published online Nov. 5, 2012; doi:10.1021/jm3011178 Contact: Robert Day, University of Sherbrooke, Sherbrooke, Quebec, Canada e-mail: robert.day@usherbrooke.ca</p>
Cardiovascular disease				
Myocardial infarction (MI)	p75 Neurotrophin receptor (p75 NTR); nerve growth factor (NGF)	<p>Patient and mouse studies suggest antagonizing p75 NTR could help treat MI. In hearts of patients that had fatal MI and in a mouse model of ischemia/reperfusion injury, levels of the NGF precursor proNGF were higher in cardiac myocytes and levels of p75 NTR were greater in arterioles than those in hearts from patients who died of non-cardiac-related causes and in sham-operated mice. In mice with impaired processing of proNgf into mature Ngf, vascular permeability and cardiomyopathy were greater than those in mice with normal proNgf processing. Next steps include identifying small molecules and biologics that target proNGF.</p> <p>At least seven companies have compounds targeting NGF in clinical and preclinical testing for neurology indications.</p> <p>SciBX 5(46); doi:10.1038/scibx.2012.1206 Published online Nov. 29, 2012</p>	Patent application filed; available for licensing	<p>Siao, C.-J. <i>et al. J. Exp. Med.</i>; published online Oct. 22, 2012; doi:10.1084/jem.20111749 Contact: Barbara L. Hempstead, Weill Cornell Medical College, New York, N.Y. e-mail: blhempst@med.cornell.edu</p>

This week in therapeutics (continued)

Indication	Target/marker/ pathway	Summary	Licensing status	Publication and contact information
Endocrine/metabolic disease				
Diabetes	Glucagon-like peptide-1 receptor (GLP-1R; GLP1R); estrogen receptor	<i>In vitro</i> and mouse studies identified a stable GLP-1-estrogen conjugate that could help treat type 2 diabetes. In mice, the conjugate increased weight loss compared with GLP-1 alone and led to improved insulin sensitivity and glycemic control. In mice, estradiol or an unstable GLP-1-estrogen conjugate induced hypertrophic activity in the uterus and stimulated the growth of tumor xenografts, whereas the stable GLP-1-estrogen conjugate did not. Next steps include additional safety studies to rule out an oncogenic effect on cells that express both GLP-1R and estrogen receptor. Marcadia Biotech Inc., which was acquired by Roche in 2010, partially funded the study. SciBX 5(46); doi:10.1038/scibx.2012.1207 Published online Nov. 29, 2012	Patent application filed; exclusively licensed to Roche	Finan, B. <i>et al. Nat. Med.</i> ; published online Nov. 11, 2012; doi:10.1038/nm.3009 Contact: Matthias H. Tschöp, German Research Center for Environmental Health, Munich, Germany e-mail: matthias.tschoepp@helmholtz-muenchen.de Contact: Richard D. DiMarchi, Indiana University, Bloomington, Ind. e-mail: rdimarch@indiana.edu
Dyslipidemia; hypercholesterolemia	Proprotein convertase subtilisin/kexin type 9 (PCSK9); low-density lipoprotein receptor (LDLR)	Mouse studies suggest PCSK9 inhibitors and antibodies need to target both the full-length and cleaved versions of the protein. In a mouse liver model of Ldlr degradation, intact wild-type PCSK9 or PCSK9 cleaved by furin or hepsin each led to degradation of mouse liver Ldlr. In mice, furin-cleaved PCSK9 led to a 27% increase in cholesterol at 6 hours compared with a 35% increase for intact PCSK9, which suggests cleaved PCSK9 is still active. Ongoing work includes designing antibodies that target both cleaved and intact PCSK9. Sanofi and Regeneron Pharmaceuticals Inc. have REGN727, a human mAb targeting PCSK9, in Phase III testing to treat hypercholesterolemia. At least nine other companies have PCSK9 inhibitors in Phase II testing or earlier to treat hypercholesterolemia and other metabolic diseases. SciBX 5(46); doi:10.1038/scibx.2012.1208 Published online Nov. 29, 2012	Patent and licensing status undisclosed	Lipari, M.T. <i>et al. J. Biol. Chem.</i> ; published online Nov. 7, 2012; doi:10.1074/jbc.M112.380618 Contact: Daniel Kirchhofer, Genentech Inc., South San Francisco, Calif. e-mail: dak@gene.com
Hepatic disease				
Nonalcoholic steatohepatitis (NASH)	Protein peptidylprolyl <i>cis/trans</i> isomerase NIMA-interacting 1 (PIN1)	Mouse studies suggest inhibiting PIN1 could help treat and prevent NASH. In mice fed a NASH-inducing diet, <i>Pin1</i> knockouts had lower markers of liver injury, inflammation and fibrosis than wild-type controls. Next steps could include developing PIN1 inhibitors and evaluating them in models of NASH. SciBX 5(46); doi:10.1038/scibx.2012.1209 Published online Nov. 29, 2012	Patent and licensing status unavailable	Nakatsu, Y. <i>et al. J. Biol. Chem.</i> ; published online Oct. 29, 2012; doi:10.1074/jbc.M112.397133 Contact: Tomoichiro Asano, Hiroshima University, Hiroshima, Japan e-mail: asano-tky@umin.ac.jp

This week in therapeutics (continued)

Indication	Target/marker/ pathway	Summary	Licensing status	Publication and contact information
Infectious disease				
Viral infection	Protein tyrosine phosphatase 1B (PTP-1B; PTPN1)	<p>Cell culture and feline studies suggest PTP-1B inhibitors could increase the efficacy of interferon (IFN) therapies against viral infections. In cultured cells infected with HCV or vesicular stomatitis virus, type 1 interferon (IFN1) plus the PTP-1B inhibitor 7-CBNP decreased viral replication compared with IFN1 alone. In cats with chronic infection of feline calicivirus, submucosal injection of 7-CBNP decreased inflammation compared with that seen prior to treatment. Next steps include using 7-CBNP or other PTP-1B inhibitors in nonmouse models of viral infection, including HIV-related feline immunodeficiency virus (FIV).</p> <p>TransTech Pharma Inc.'s PTP-1B inhibitor, TTP814, is in Phase II testing to treat diabetes.</p> <p>Isis Pharmaceuticals Inc.'s ISIS-PTP1bRx, a PTP-1B antisense oligonucleotide, is in Phase I testing to treat diabetes.</p> <p>Ohr Pharmaceutical Inc.'s trodusquemine (MSI-1436), a small molecule PTP-1B inhibitor, is in Phase I testing for the same indication.</p> <p>SciBX 5(46); doi:10.1038/scibx.2012.1210 Published online Nov. 29, 2012</p>	Patented; available for licensing	<p>Carbone, C.J. <i>et al. Proc. Natl. Acad. Sci. USA</i>; published online Nov. 5, 2012; doi:10.1073/pnas.1211491109</p> <p>Contact: Serge Y. Fuchs, University of Pennsylvania, Philadelphia, Pa. e-mail: syfuchs@vet.upenn.edu</p>
Inflammation				
Inflammation	Diacylglycerol lipase- β (DAGLB); tumor necrosis factor- α (TNF- α)	<p>Mouse and <i>in vitro</i> studies suggest inhibiting DAGLB could help prevent inflammation. <i>In vitro</i> studies identified a 1,2,3-triazole urea-based molecule that selectively inhibited the serine hydrolase DAGLB with midnanomolar IC₅₀ values. In mice, the DAGLB inhibitor decreased levels of arachidonic acid-derived prostaglandins in macrophages compared with an inactive control compound. In lipopolysaccharide (LPS)-stimulated macrophages isolated from DAGLB inhibitor-treated mice, Tnf-α production was lower than that in macrophages obtained from mice treated with the control compound. Next steps include looking at the phenotype of pharmacological and genetic disruption of DAGLB models of inflammation and optimizing DAGLB, DAGLA, and dual DAGLB and DAGLA inhibitors.</p> <p>Corresponding author Benjamin Cravatt is a founder of Abide Therapeutics Inc., which is developing serine hydrolase inhibitors.</p> <p>SciBX 5(46); doi:10.1038/scibx.2012.1211 Published online Nov. 29, 2012</p>	Patented; licensed to an undisclosed company	<p>Hsu, K.-L. <i>et al. Nat. Chem. Biol.</i>; published online Oct. 28, 2012; doi:10.1038/nchembio.1105</p> <p>Contact: Benjamin F. Cravatt, The Scripps Research Institute, La Jolla, Calif. e-mail: cravatt@scripps.edu</p>

This week in therapeutics (continued)

Indication	Target/marker/ pathway	Summary	Licensing status	Publication and contact information
Neurology				
Alzheimer's disease (AD)	Nuclear factor of activated T cells cytoplasmic calcineurin-dependent (NFATc); calcineurin	<p>Mouse studies suggest astrocyte-specific delivery of the synthetic peptide VIVIT could help to treat AD. An adeno-associated virus (AAV) vector containing an astrocyte-specific promoter was used to express VIVIT, which inhibits the NFATc and calcineurin signaling pathway. In a mouse model of AD, hippocampal injection of the vector during early stages of disease progression led to astrocyte-specific expression of VIVIT and increased cognitive and synaptic function compared with vehicle. Next steps include testing the VIVIT-expressing vector in mice with late-stage AD and in an aging canine model of AD.</p> <p>SciBX 5(46); doi:10.1038/scibx.2012.1212 Published online Nov. 29, 2012</p>	Unpatented; licensing status not applicable	<p>Furman, J.L. <i>et al. J. Neurosci.</i>; published online Nov. 14, 2012; doi:10.1523/JNEUROSCI.2323-12.2012 Contact: Christopher M. Norris, University of Kentucky College of Medicine, Lexington, Ky. e-mail: cnorr2@email.uky.edu</p>
Parkinson's disease (PD)	Nitric oxide (NO); PTEN induced putative kinase 1 (PINK1)	<p>Cell culture studies suggest restoring NO signaling could help correct mitochondrial dysfunction in neurodegenerative diseases such as mutant PINK1-associated PD. In <i>Pink1</i> knockout mouse dopaminergic neurons, a bioactive component of ginseng called Re increased NO signaling compared with no treatment and rescued the dysfunction in mitochondrial cytochrome c oxidase activity. Next steps include evaluating the compound in <i>in vivo</i> models of PD and Alzheimer's disease that include a mitochondrial impairment component.</p> <p>SciBX 5(46); doi:10.1038/scibx.2012.1213 Published online Nov. 29, 2012</p>	Patent application filed; available for licensing from Ewha Womans University	<p>Kim, K.-H. <i>et al. J. Biol. Chem.</i>; published online Nov. 9, 2012; doi:10.1074/jbc.M112.408146 Contact: Jin H. Son, Ewha Womans University, Seoul, South Korea e-mail: hjson@ewha.ac.kr</p>

This week in techniques

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

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

Approach	Summary	Licensing status	Publication and contact information
Assays & screens			
Assays for resistance assessment by binding competition	Assays for resistance assessment by binding competition could be useful for identifying drug-resistant viral strains. In a proof-of-concept study, labeled Relenza zanamivir was used as a probe in competitive binding assays to identify influenza strains that were resistant to Tamiflu oseltamivir. In 137 seasonal H1N1 clinical isolates from Taiwanese patients, the binding assay showed that Tamiflu-resistant strains began to emerge in mid-2008. Next steps include developing an assay system based on the approach and running clinical validation studies. GlaxoSmithKline plc markets Relenza to treat and prevent influenza. Gilead Sciences Inc. and Roche market Tamiflu to treat and prevent influenza. SciBX 5(46); doi:10.1038/scibx.2012.1214 Published online Nov. 29, 2012	Patent application filed by Academia Sinica; available for licensing	Cheng, T.-J.R. <i>et al. Angew. Chem. Int. Ed.</i> ; published online Nov. 13, 2012; doi:10.1002/anie.201204062 Contact: Chi-Huey Wong, Academia Sinica, Taipei, Taiwan e-mail: chwong@gate.sinica.edu.tw Contact: Yih-Shyun E. Cheng, same affiliation as above e-mail: ysecheng@gate.sinica.edu.tw Contact: Jim-Min Fang, National Taiwan University, Taipei, Taiwan e-mail: jmfang@ntu.edu.tw
Disease models			
Implantable hydrogel scaffold for simulating the bone marrow microenvironment	An implantable hydrogel that simulates the bone marrow microenvironment could help the development of new therapies to treat hematological malignancies. An acrylamide-based hydrogel scaffold was manufactured and seeded with human bone marrow stromal cells and subcutaneously implanted into mice. The scaffolds attracted endogenous hematopoietic stem cells and intravenously injected human leukemic cells that were imaged via intravital confocal microscopy. Next steps include using the system to model the development of blood and tissue cancers. SciBX 5(46); doi:10.1038/scibx.2012.1215 Published online Nov. 29, 2012	Unpatented; available for collaboration	Lee, J. <i>et al. Proc. Natl. Acad. Sci. USA</i> ; published online Nov. 12, 2012; doi:10.1073/pnas.1208384109 Contact: Biju Parekkadan, Harvard Medical School and Shriners Hospital for Children, Boston, Mass. e-mail: biju_parekkadan@hms.harvard.edu
Long-term, prion-infected cultures of organotypic cerebellar slices to monitor neurodegeneration	Long-term, prion-infected organotypic cerebellar slices could be used to identify neuroprotective therapeutics more accurately than cell-based assays. In five-week-old, prion-infected murine organotypic cerebellar slices, progressive spongiform neurodegeneration developed, closely recapitulating prion disease. In the model, compounds known to suppress prion replication <i>in vivo</i> had neuroprotective effects, whereas those known to only suppress prion replication in cell culture did not. Next steps include using the system to screen for neuroprotective molecules. SciBX 5(46); doi:10.1038/scibx.2012.1216 Published online Nov. 29, 2012	Unpatented; licensing status not applicable	Falsig, J. <i>et al. PLoS Pathog.</i> ; published online Nov. 1, 2012; doi:10.1371/journal.ppat.1002985 Contact: Adriano Aguzzi, Institute of Neuropathology, Zurich, Switzerland e-mail: adriano.aguzzi@usz.ch
Mouse model for typhoid fever	A mouse model for gastroenteritis and typhoid fever caused by <i>Salmonella enterica</i> Typhi could be used to evaluate therapeutic candidates. Mice with a genetic deletion of <i>toll-like receptor 11</i> (<i>Tlr11</i>), a mouse-specific innate immune system receptor that binds to a protein on the surface of <i>S. enterica</i> Typhi, developed enteropathic bacterial infection and had decreased survival compared with wild-type controls. <i>Tlr11</i> knockout mice immunized with heat-killed <i>S. enterica</i> Typhi developed immunity to subsequent infection with live bacteria. Next steps could include using the mouse model to evaluate therapeutic candidates. SciBX 5(46); doi:10.1038/scibx.2012.1217 Published online Nov. 29, 2012	Patent and licensing status undisclosed	Mathur, R. <i>et al. Cell</i> ; published online Oct. 26, 2012; doi:10.1016/j.cell.2012.08.042 Contact: Sankar Ghosh, Columbia University, New York, N.Y. e-mail: sg2715@columbia.edu

This week in techniques (continued)

Approach	Summary	Licensing status	Publication and contact information
Drug platforms			
Inducing vascular endothelial cells from amniotic stem cells	Cell culture and mouse studies identified methods to reprogram amniotic cells into vascular endothelial cells. In human amniotic cells, transfection with three transcription factors—ETS variant gene 2 (ETV2), friend leukemia virus integration 1 (FLI1) and v-ets erythroblastosis virus E26 oncogene homolog (ERG)—plus competitive inhibition of transforming growth factor- β (TGFB; TGF- β) led to formation of cells with morphological, genetic and functional similarities to natural vascular endothelial cells. In mice with damaged livers, implantation of the induced vascular endothelial cells led to growth of functional hepatic blood vessels, whereas implantation of control cells did not. Next steps could include testing the effect of induced vascular endothelial cells in mouse models of disease and scaling up production of the cells. SciBX 5(46); doi:10.1038/scibx.2012.1218 Published online Nov. 29, 2012	Patent and licensing status unavailable	Ginsberg, M. <i>et al. Cell</i> ; published online Oct. 18, 2012; doi:10.1016/j.cell.2012.09.032 Contact: Shahin Rafii, Weill Cornell Medical College, New York, N.Y. e-mail: srafi@med.cornell.edu
Method for generating disulfide-linked cyclic peptides	A method for generating disulfide-linked cyclic peptides could be useful as a platform for identifying new therapeutic leads. The method involves designing peptides with cysteine residues at appropriate intervals that result in their spontaneous folding into bicyclic or tricyclic structures. Next steps include identifying specific multicyclic scaffolds with high stability and resistance to degradation that can then be used to screen for therapeutic leads. SciBX 5(46); doi:10.1038/scibx.2012.1219 Published online Nov. 29, 2012	Unpatented; licensing status not applicable	Wu, C. <i>et al. Nat. Chem.</i> ; published online Oct. 28, 2012; doi:10.1038/nchem.1487 Contact: Marc A. Gauthier, Swiss Federal Institute of Technology Zurich (ETHZ), Zurich, Switzerland e-mail: marc.gauthier@pharma.ethz.ch Contact: Jean-Christophe Leroux, same affiliation as above e-mail: jleroux@ethz.ch
Markers			
Core-binding factor runt domain α -subunit 2 translocated to 3 (CBFA2T3)-GLIS family zinc finger 2 (GLIS2) fusion protein as a biomarker for non-Down syndrome acute megakaryoblastic leukemia (non-DS-AMKL)	Genetic and <i>in vitro</i> studies suggest the CBFA2T3-GLIS2 fusion protein could be useful as a biomarker in pediatric non-DS-AMKL. In patients with pediatric non-DS-AMKL, 7 of 14 patients showed an inversion in chromosome 16 that led to expression of a CBFA2T3-GLIS2 fusion protein. In 12 pediatric patients carrying the mutations, 5-year survival was lower than that for 28 pediatric patients without the mutation. In murine hematopoietic progenitor cells, expression of the fusion protein increased self-renewal capacity compared with expression of GLIS2 alone, suggesting the fusion protein contributes to leukemogenesis. Next steps could include additional validation studies. SciBX 5(46); doi:10.1038/scibx.2012.1220 Published online Nov. 29, 2012	Patent and licensing status unavailable	Gruber, T.A. <i>et al. Cancer Cell</i> ; published online Nov. 13, 2012; doi:10.1016/j.ccr.2012.10.007 Contact: James R. Downing, St. Jude Children's Research Hospital, Memphis, Tenn. e-mail: james.downing@stjude.org
PD-1 receptor (PDCD1; PD-1; CD279)-expressing T cells for HPV-positive head and neck cancer prognosis	<i>In vitro</i> and mouse studies suggest levels of PD-1-expressing T cells could be useful as a prognostic marker and help guide treatment for HPV-positive head and neck cancer. In 32 patients with HPV-positive head and neck cancers, survival rates and levels of PD-1-expressing T cells were higher than those for 32 patients with HPV-negative cancers. In a mouse HPV tumor model, an antibody targeting the PD-1 ligand programmed cell death 1 ligand 1 (CD274 molecule; PD-L1; B7-H1) increased the antitumor effect of an HPV cancer vaccine targeting E7 transforming protein (human papillomavirus-16; HpV16gp1) compared with control antibodies. Next steps include validating the biomarker findings and testing anti-PD-1 antibodies in clinical trials. At least eight companies have antibodies targeting PD-1 or PD-L1 in Phase II testing or earlier to treat various cancers. SciBX 5(46); doi:10.1038/scibx.2012.1221 Published online Nov. 29, 2012	Findings unpatented; licensing not applicable	Badoual, C. <i>et al. Cancer Res.</i> ; published online Nov. 7, 2012; doi:10.1158/0008-5472.CAN-12-2606 Contact: Eric Tartour, Georges Pompidou European Hospital, Paris, France e-mail: eric.tartour@egp.aphp.fr

This week in techniques (continued)

Approach	Summary	Licensing status	Publication and contact information
Secreted frizzled-related protein 4 (SFRP4) as a marker of islet dysfunction	<p>Mouse and human studies suggest SFRP4 could be useful as a biomarker to detect islet dysfunction in type 2 diabetes. Gene expression data of islets from 48 humans showed that high levels of SFRP4 were associated with multiple markers of type 2 diabetes, such as increased hemoglobin A1c (HbA1c) levels and decreased insulin secretion. In mouse and human pancreatic islets, SFRP4 decreased glucose-induced insulin secretion compared with no treatment. In mice, SFRP4 injections decreased insulin secretion and increased glucose intolerance compared with saline injections. Next steps include validating SFRP4 as a marker in a larger cohort.</p> <p>SciBX 5(46); doi:10.1038/scibx.2012.1222 Published online Nov. 29, 2012</p>	Patent application filed; available for licensing from the Lund University Diabetes Centre	<p>Mahdi, T. <i>et al. Cell Metab.</i>; published online Nov. 6, 2012; doi:10.1016/j.cmet.2012.10.009 Contact: Anders H. Rosengren, Lund University, Malmo, Sweden e-mail: anders.rosengren@med.lu.se</p>

Company and institute index

A		O				J	
Abbott Laboratories	9	Ohr Pharmaceutical Inc.	14	Cyclophosphamide	1	Januvia	3
Abide Therapeutics Inc.	14	Ono Pharmaceutical Co. Ltd.	3	Cystic fibrosis transmembrane conductance regulator	9	K	
Academia Sinica	16	P		Cytochrome c	15	Kalydeco	10
Anacor Pharmaceuticals Inc.	5	Pfizer Inc.	2,4,9	D		L	
AstraZeneca plc	4,9	Proteostasis Therapeutics Inc.	10	DAGLA	4	Lars	5
Atlas Venture	4	R		DAGLB	14	Latondaine A	9
B		Regeneron Pharmaceuticals Inc.	13	Daptomycin	4	Latondaine B (ethyl)	9
Basilea Pharmaceutica AG	5	Rib-X Pharmaceuticals Inc.	4	Delafloxacin	4	LDLR	13
Biomedical Advanced Research and Development Authority	4	Roche	13,16	Diacylglycerol lipase β	14	Leucyl-tRNA synthetase	5
Broad Institute of MIT	5	S		Dipeptidyl peptidase-4	3	Leurs	5
C		Sanofi	5,13	Diterpenoid triepoxide	7	Linezolid	4
Cancer Research UK	9	T		DNA gyrase	5	Lipopolysaccharide	14
Cempra Inc.	5	Takeda Pharmaceutical Co. Ltd.	3	DPP-4	3	Low-density lipoprotein receptor	13
Clovis Oncology Inc.	9	Tetraphase Pharmaceuticals Inc.	5	E		LPS	14
Cubist Pharmaceuticals Inc.	4	Theravance Inc.	4	E7 transforming protein	17	M	
Curetis AG	6	TransTech Pharma Inc.	14	Eravacycline	5	MALT1	11
Cystic Fibrosis Foundation	10	Trius Therapeutics Inc.	4	ERG	17	Minnelide	7
Cystic Fibrosis Foundation Therapeutics Inc.	10	U		E selectin	1	MSI-1436	14
D		UniQuest Pty. Ltd.	2	Estradiol	13	Mucosa associated lymphoid tissue lymphoma translocation gene 1	11
Dana-Farber Cancer Institute	3	University of British Columbia	10	Estrogen	13	MurB	5
Digna Biotech S.L.	11	University of Minnesota	7	Estrogen receptor	13	N	
E		University of Queensland	1	ETS variant gene 2	17	Nerve growth factor	12
Eli Lilly and Co.	7	V		ETV2	17	NFATc	15
Emory University	12	Vertex Pharmaceuticals Inc.	9	F		NF- κ B	7
Erasmus Medical Center	7	F60008	7	NGF	12
Ewha Womans University	15	Target and compound index		Fluoroketolide	5	Nitric oxide	15
F		1,2,3-Triazole urea	14	Friend leukemia virus integration 1	17	NO	15
Food and Drug Administration	4	5-Fluorouracil	1	FLI1	17	Nuclear factor of activated T cells cytoplasmic calcineurin-dependent	15
Forest Laboratories Inc.	4	5-FU	1	Furin	12,13	O	
G		7-CBNP	14	G		Olaparib	9
Gilead Sciences Inc.	16	A		Gemcitabine	7	Oseltamivir	16
GlaxoSmithKline plc	5,9,16	ABT-888	9	Gemzar	7	P	
GlycoMimetics Inc.	1	Alkaline phosphatase	7	GLIS2	17	p75 Neurotrophin receptor	12
H		APOA1	11	GLIS family zinc finger 2	17	p75 NTR	12
Harvard Medical School	3	Apolipoprotein A-1	11	Glucagon-like peptide-1 receptor	13	PACE4	12
I		Arachidonic acid	14	GLP-1	13	PARP	9
Indiana University School of Medicine	3	AURKA	11	GLP-1R	13	PARP-1	9
Innovative Medicines Initiative	4	AURKB	11	GLP1R	13	PARP-2	9
Isis Pharmaceuticals Inc.	14	Aurora-A	11	GMI-1070	1	PARP-3	9
J		Aurora-B	11	GSK1322322	5	PARP-6	9
Johnson & Johnson	3,5	Aurora kinase B	11	GSK2140944	5	PCSK6	12
L		AZD2281	9	GSK2251052	5	PCSK9	13
Lund University Diabetes Centre	18	B		H		PD-1	17
M		B7-H1	17	HbA1c	18	PD-1 receptor	17
Marcadia Biotech Inc.	13	Bortezomib	3	Heat shock protein 70	7	PDCD1	17
Massachusetts Institute of Technology	9	C		Hemoglobin A1c	18	Pdf	5
Mater Medical Research Institute	1	Calcineurin	15	Hepsin	13	PD-L1	17
McGill University	9	Carbapenem	5	HpV16gp1	17	Peptide deformylase	5
Merck & Co. Inc.	3	CBFA2T3	17	Hsp70	7	PGAM1	12
Minneamrita Therapeutics LLC	7	CD62E	1	Human papillomavirus-16	17	Phosphoglycerate mutase 1	12
		CD62P	1	I		PIN1	13
		CD274 molecule	17	IFN	14	PINK1	15
		CD279	17	IFN1	14	Poly(ADP-ribose) polymerase	9
		Ceftaroline	4	IL-15	11	Porin	5
		Cephalosporin	5	IL-15RA	11	Programmed cell death 1 ligand 1	17
		CFTR	9	IL-15 receptor α -chain	11		
		CO-338	9	Interferon	14		
		Core-binding factor runt domain α -subunit 2 translocated to 3	17	ISIS-PTP1bRx	14		
		Cubicin	4	Ivacaftor	10		

ProNGF	12	S	Th17	11	U	
Proprotein convertase subtilisin/ kexin type 6	12	Secreted frizzled-related protein 4	T helper type 17	11	UDP-N- acetylenolpyruvoylglucosamine reductase	5
Proprotein convertase subtilisin/ kexin type 9	13	SELE	<i>Tlr11</i>	18		
Protein peptidylprolyl <i>cis/trans</i> isomerase NIMA-interacting 1	13	SELP	TNF- α	1		
Protein tyrosine phosphatase 1B	14	SFRP4	<i>Toll-like receptor 11</i>	1		
PTEN induced putative kinase 1	15	Sitagliptin	Topoisomerase IIA	18		
PTP-1B	14	Solithromycin	Topoisomerase IV	3		
PTPN1	14	T	TRAIL	5		
R		Tamiflu	Transforming growth factor- β	17		
REGN727	13	Tedizolid	Triptolide	16		
Relenza	16	Teflaro	Trodesquimine	6		
Rucaparib	9	Telavacin	TTP814	4		
		Tetracycline	Tumor necrosis factor- α	4		
		TGFB	Tumor necrosis factor-related apoptosis-inducing ligand	5		
		TGF- β	Type 1 interferon	17		
				17		
				11		
				16		
				14		
				16		
				5		
				5	V	
				8	Velcade	3
				17	Veliparib	9
				7	v-Ets erythroblastosis virus E26 oncogene homolog	17
				14	Vibativ	4
				14	VIVIT	15
				14	VX-809	10
				14	Z	
				8	Zanamivir	16
				14	Zyvox	4