

THIS WEEK

ANALYSIS

COVER STORY

1 Reviving Ras

Genentech and Vanderbilt teams have independently used fragment-based drug discovery to identify a new small molecule binding site that blocks activation of Ras, a highly prevalent oncoprotein that has previously been considered undruggable. The results could reinvigorate drug discovery efforts against the target.

TARGETS & MECHANISMS

4 Cooling down AD

A Johns Hopkins University team has clinical proof-of-concept data for slowing the progression of Alzheimer's disease by reducing activity in the hippocampus with antiepileptic drugs. AgeneBio has licensed the IP and is planning a Phase II trial of an antiepileptic to prevent AD.

5 Getting around peripartum cardiomyopathy

A Harvard Medical School–led team has shown that a soluble form of FLT1 causes about one-third of peripartum cardiomyopathy cases—those associated with preeclampsia. Ongoing studies are seeking to identify small molecule inhibitors of the protein and determine whether the mechanism also underlies the other two-thirds of cases.

6 Getting selective for γ

Cellzome and Exelixis have independently designed the first highly selective inhibitors of the γ -isoform of PI3K. Exelixis hopes to out-license its inhibitors, whereas the recent acquisition of Cellzome by GlaxoSmithKline gives the pharma a new class of compounds for inflammatory and autoimmune diseases.

THE DISTILLERY

10 This week in therapeutics

Treating melanoma by antagonizing PREX2; preventing thrombosis with PDI inhibitors; ameliorating hyperalgesia in diabetic neuropathy by blocking methylglyoxal; and more...

16 This week in techniques

High throughput sequencing of TCRs to detect minimal residual disease in T cell acute lymphoblastic leukemia; a proteomic method for developing rational combinations of kinase inhibitors; synthesis of biologically active meroterpenoids; and more...

INDEXES

18 Company and institution index

18 Target and compound index

Reviving Ras

By Joanne Kotz, Senior Editor

Activated Ras proteins are among the most notorious oncoproteins, but thus far they have proven undruggable. Now, teams at **Roche's Genentech Inc.** unit and at **Vanderbilt University School of Medicine** have independently used fragment-based drug discovery to identify a new small molecule binding site that blocks Ras activation.^{1,2}

The results could reinvigorate drug discovery efforts against the target. Remaining hurdles include developing more potent inhibitors and testing whether optimized molecules block mutant Ras-driven cancers.

Ras proteins are central regulators of cell growth and proliferation. In response to growth factors, these GTP binding proteins are turned on by guanine nucleotide exchange factors (GEFs) such as son of sevenless homolog 1 (SOS1).

Collectively, mutations in the three isoforms of Ras—*HRAS* (*v-Harvey rat sarcoma viral oncogene homolog*), *K-Ras* and *NRAS* (*neuroblastoma Ras viral (v-Ras) oncogene*)—occur in over 20% of all cancers.

Indeed, Guowei Fang, a senior scientist in research oncology at Genentech, noted that *Ras* “is the most frequently mutated oncogene in human tumors and correlates with poor prognosis of patients. But from the druggability side, this target has been worked on by nearly every pharma over the last 20 years with little benefit.”

Fang said advances in using fragments—pieces of small molecules—in drug discovery “made us give this a second thought.”

Calling on fragments

Of the three Ras isoforms, K-Ras is the most frequently dysregulated, with activating mutations occurring in about 80% of pancreatic cancers, 40% of colon cancers and 25% of lung cancers.

Stephen Fesik, who headed the Vanderbilt team, said when he joined the university in 2009 and set out to work on six validated but challenging cancer targets, K-Ras was on the list. Fesik is professor of biochemistry, pharmacology and chemistry and chair in cancer research in the Vanderbilt University School of Medicine.

Before Vanderbilt, Fesik was divisional VP of cancer research at **Abbott Laboratories**. While at Abbott, Fesik led the effort to develop inhibitors of the B cell lymphoma 2 (BCL-2; BCL2) family of proteins, which are challenging protein-protein interaction targets. The resulting inhibitor, navitoclax (ABT-263), is partnered with Genentech. The compound is in a Phase II trial in combination with Rituxan rituximab in chronic lymphocytic leukemia (CLL) and in a Phase I/II trial as a single agent in relapsed or refractory CLL or other lymphoid malignancies.

**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**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 5333Chadds Ford
223 Wilmington-West Chester Pike
Chadds Ford, PA 19317
T: +1 610 558 1873Chicago
20 N. Wacker Drive, Suite 1465
Chicago, IL 60606-2902
T: +1 312 755 0798Oxford
287 Banbury Road
Oxford OX4 7JA
United 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 Inchcombe, 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.

To tackle K-Ras, both the Vanderbilt and Genentech teams turned to fragment-based drug discovery.

Using this approach, small libraries of fragments that weigh 100–300 Da are screened by sensitive structural or biophysical methods that identify molecules that bind a target with high micromolar to low millimolar affinities.

In contrast, high throughput screening typically involves sifting through very large libraries of small molecules weighing 300–600 Da to identify hits with affinities or activities in the nanomolar to low micromolar range.

Fesik's team screened 11,000 fragments using NMR and identified 140 that bound to K-Ras.

The Genentech team also used NMR, screening 3,300 fragments and identifying 25 confirmed hits.

In both cases, the groups obtained co-crystal structures that revealed the fragments bound at the interface with SOS1. *In vitro* assays showed the fragments blocked SOS1-mediated activation of K-Ras with mid-

to high-micromolar IC_{50} values. This newly identified binding site is conserved among isoforms, and both groups confirmed that the fragments bound to wild-type K-Ras, mutant K-Ras and HRAS.

The Genentech group's lead fragment reduced epidermal growth factor (EGF)-mediated activation of Ras proteins, which is known to be mediated by SOS1, with a mid-micromolar EC_{50} in human cells.

Fang added that in parallel with fragment-based screening, Genentech conducted a traditional high throughput screen of the company's full library—over one million compounds—in a biochemical assay of Ras function. Fang said the screen yielded no workable hits.

Results from Genentech were published in the *Proceedings of the National Academy of Sciences*. The Vanderbilt team published its findings in *Angewandte Chemie International Edition*.

"These compounds are very early, but it's really very exciting that groups have identified novel fragments binding to one of the so-called undruggable targets and importantly solved crystal structures with ligands bound," said Martin Drysdale, professor and head of the drug discovery program at **The Beatson Institute for Cancer Research**.

He said his group also is targeting K-Ras via fragment-based approaches. The work has not yet been published. Drysdale previously was deputy research director at the fragment-based and structure-based drug discovery company **Vernalis plc**.

"This is an incredibly important advance. You can now take another look at Ras applying modern techniques, including fragments and crystallography, and hone in on trying to find inhibitors," said John Lyons, VP of translational research at **Astex Pharmaceuticals Inc.** "Pharmas will doubtless want to give this a go. It's such a high-value target that no one will want to be left out."

Lyons declined to disclose whether Astex would now be pursuing Ras proteins.

"This is an incredibly important advance. You can now take another look at Ras applying modern techniques, including fragments and crystallography, and hone in on trying to find inhibitors."

—John Lyons,
Astex Pharmaceuticals Inc.

Next up, mutant K-Ras

An open question is whether blocking Ras activation—rather than blocking Ras activity—will have an impact in mutant *K-Ras*-driven cancers.

“These results have shown that you can inhibit the activation of K-Ras but have not yet shown that you can inhibit mutant K-Ras signaling,” noted Lyons.

“These compounds are very early, but it’s really very exciting that groups have identified novel fragments binding to one of the so-called undruggable targets and importantly solved crystal structures with ligands bound.”

—Martin Drysdale,
The Beatson Institute for
Cancer Research

Although the fragments described in the papers block Ras activation, future optimized molecules could block both activation and downstream signaling.

“Where these compounds bind Ras is close to the Ras-SOS1 interface but also close to the Ras-effector interface,” said Weiru Wang, a senior scientist in Genentech’s

structural biology department. Thus, he said it may be possible to design a molecule that also antagonizes the interaction of Ras with its various downstream effectors.

Even if an inhibitor of mutant K-Ras activity cannot be developed, a molecule that only blocks wild-type Ras may still have activity in mutant *K-Ras*-driven cancers.

For example, in mouse models of mutant *K-Ras*-driven pancreatic tumors, both mutant K-Ras and wild-type HRAS are required for tumor growth.³ Fang added that Genentech also has internal data supporting a co-dependency between mutant K-Ras and wild-type Ras in a subset of mutant *K-Ras*-driven cancers. In this case, he added, a pan-selective Ras inhibitor would be the goal.

Finally, inhibitors of Ras activation could be useful in cancers

with alterations upstream of Ras. Fang noted that in EGF receptor (EGFR)-driven cancers, inhibiting Ras activation would block a major downstream signaling pathway.

The Vanderbilt and Genentech teams are now working to optimizing the potency of their inhibitors and to develop inhibitors of mutant K-Ras.

Fesik said he has had discussions with companies, but “most would like to see very potent molecules that are active in cells to take down the risk. Frankly, the jury’s still out on whether we can do this.”

Fesik declined to disclose the patent status of the work but said the project is available for licensing or partnering.

Genentech declined to disclose the patenting status of the work. It is not available for licensing.

Kotz, J. *SciBX* 5(21); doi:10.1038/scibx.2012.536
Published online May 24, 2012

REFERENCES

1. Sun, Q. *et al. Angew. Chem. Int. Ed.*; published online May 8, 2012; doi:10.1002/anie.201201358
Contact: Stephen W. Fesik, Vanderbilt University School of Medicine, Nashville, Tenn.
e-mail: stephen.fesik@vanderbilt.edu
2. Maurer, T. *et al. Proc. Natl. Acad. Sci. USA*; published online March 19, 2012; doi:10.1073/pnas.1116510109
Contact: Guowei Fang, Genentech Inc., South San Francisco, Calif.
e-mail: fang.guowei@gene.com
Contact: Weiru Wang, same affiliation as above
e-mail: wang.weiru@gene.com
3. Lim, K.-H. *et al. Nature* **452**, 646–649 (2008)

COMPANIES AND INSTITUTIONS MENTIONED

Abbott Laboratories (NYSE:ABT), Abbott Park, Ill.

Astex Pharmaceuticals Inc. (NASDAQ:ASTX), Dublin, Calif.

The Beatson Institute for Cancer Research, Glasgow, U.K.

Genentech Inc., South San Francisco, Calif.

Roche (SIX:ROG; OTCQX:RHHBY), Basel, Switzerland

Vanderbilt University School of Medicine, Nashville, Tenn.

Vernalis plc (LSE:VER), Winnersh, U.K.

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

Cooling down AD

By Lev Osherovich, Senior Writer

A team from **The Johns Hopkins University** has clinical proof of concept for an unconventional approach to slowing the progression of Alzheimer's disease—reducing activity in the hippocampus with antiepileptic drugs.¹ Based on the findings, **AgeneBio Inc.** has licensed patent applications from the university on lowering brain activity with antiepileptic drugs to prevent AD.

The standard view of AD etiology holds that the disease results from neuronal loss in the hippocampus caused by aggregated β -amyloid ($A\beta$). The hippocampus normally facilitates memory formation and recall, but the brain region degenerates early during AD, causing lapses in short-term memory.

Multiple groups including a JHU team led by Michela Gallagher had previously found evidence of abnormally high activity in the hippocampus in patients with AD and in preclinical models of AD,² but it was unclear whether the excess activity was a cause or consequence of the disease.

Now, Gallagher's group has shown that reducing hippocampal activity with the antiepileptic drug levetiracetam actually improved memory task performance in patients with mild cognitive impairment (MCI), a condition that precedes full-blown AD.

"The story of excessive hippocampal activity in mild cognitive impairment patients has been known for some years," said Gallagher, who is a professor of psychology and neuroscience. "People had previously seen this as evidence that because memory is failing, the hippocampus is compensating by doing extra work."

The new study provides the strongest evidence yet in favor of the hypothesis that excessive hippocampal activity drives AD progression, rather than the other way around.

It has been difficult to test the relationship between epilepsy and AD in the clinic because many patients with AD experience epilepsy-like seizures, and many patients with epilepsy experience AD-like memory problems.

Other researchers have seen evidence that $A\beta$ aggregates can induce an epilepsy-like state of hippocampal hyperexcitability,³ but the relationship between $A\beta$ and epilepsy-like hippocampal activity remains murky.

Gallagher thinks that focusing on $A\beta$ is a red herring. Instead, she advocates normalizing the hyperactivity of hippocampal neurons by targeting upstream neurons that are known to go awry in epilepsy.

Speak, memory

Gallagher's team used MRI to visualize hippocampal activity in 17 patients with MCI and 17 age-matched controls. In image-matching tasks that required short-term recall, patients had impaired performance and higher levels of activity in the dentate gyrus and CA3 hippocampal regions compared with controls.

"The story of excessive hippocampal activity in mild cognitive impairment patients has been known for some years. People had previously seen this as evidence that because memory is failing, the hippocampus is compensating by doing extra work."

—Michela Gallagher,
The Johns Hopkins University

Next, the group treated the patients with a low dose of Keppra levetiracetam, a synaptic vesicle protein (SV2A) ligand marketed by **UCB Group** for partial-onset seizures, myoclonic seizures and primary generalized tonic-clonic seizures.

A two-week course of the drug decreased hippocampal activity during the memory task ($p=0.022$) compared with placebo and produced a modest but significant improvement in patients' performance at image matching ($p=0.026$). No difference was seen between the groups two weeks after dosing was stopped.

The findings were reported in *Neuron*. JHU has filed patents on using antiepileptic drugs to treat AD and has licensed the IP to AgeneBio, which Gallagher founded in 2008.

Lennart Mucke, professor of neurology and neuroscience at the **University of California, San Francisco** and director of the **Gladstone Institute of Neurological Disease**, said Gallagher's findings are in line with unpublished preclinical studies in his own laboratory.

He said clinical evidence of epilepsy-like hyperactivity in the brains of patients with AD has led him and Gallagher to investigate the effect of epilepsy drugs in rodent models of the disease.

"Levetiracetam turns out to be efficacious at suppressing abnormal brain wave activity in mouse models of AD, where it is also beneficial in terms of synaptic function and cognitive impairment," said Mucke.

Two big unknowns are the mechanism by which excessive hippocampal activity contributes to AD and how levetiracetam interferes with the disease process.

According to Gallagher, hyperexcitability of hippocampal neurons arises from age-related dysfunction in upstream inhibitory interneurons that develops independently of $A\beta$ -related AD pathology. In this view, hippocampal activity increases as a natural consequence of aging, but in some people the excess activity combines with AD mechanisms to render the hippocampus especially sensitive to the effects of aberrant $A\beta$ and microtubule-associated protein- τ (MAPT; TAU; FTDP-17), which is another AD-linked protein.

"My view is that the hippocampal hyperexcitability is a permissive factor that occurs in the background of other disease processes" such as $A\beta$ and TAU aggregation, said Gallagher.

Further preclinical studies of levetiracetam's effects could uncover how the drug affects well-validated biomarkers of AD such as $A\beta$ and TAU levels, said John Cirrito, assistant professor of neurology at the **Washington University in St. Louis**.

"One possibility is that the drug is directly suppressing $A\beta$ levels, but there is no evidence for that yet," said Cirrito.

"This drug has several modes of action," said Mucke. "One is that it binds to SV2A and could change the release of neurotransmitters. It's also reported to affect glutamate transporters, potentially counteracting excitatory activity caused by glutamate."

Commercial plans

Gallagher thinks the antiepileptic strategy is ready for broader clinical
(Continues on p. 5)

Getting around peripartum cardiomyopathy

By Michael J. Haas, Senior Writer

A Harvard Medical School–led team has shown that a soluble form of VEGF receptor 1 causes about one-third of peripartum cardiomyopathy cases—those associated with preeclampsia.¹ Ongoing studies are seeking to identify small molecule inhibitors of the protein and determine whether the mechanism also underlies the other two-thirds of cases.

Peripartum cardiomyopathy (PPCM) is a form of heart failure that affects about 1 in 1,000 peripartum women. The disease is usually diagnosed a few weeks postpartum, and current treatments are limited to standard therapies for heart failure such as β -blockers and angiotensin-converting enzyme (ACE) inhibitors.

A known risk factor for PPCM is preeclampsia, a condition involving hypertension and proteinuria that occurs in about 5% of all pregnant women but in about 33% of pregnant women with PPCM. The connection between the two diseases and the mechanism of PPCM is poorly understood.

The Harvard Medical School (HMS) team did not set out to investigate the cause of PPCM but instead stumbled upon it serendipitously while investigating the proangiogenic functions of peroxisome proliferation–activated receptor- γ coactivator 1 α (PPARGC1A; PGC-1 α) in the heart.

The researchers were breeding heart-specific *Pgc-1 α* knockout mice and noticed knockout females died after delivering only one or two

litters, whereas wild-type females delivered five or more litters without incident. Compared with knockout males, or knockout females that had not yet been pregnant, the postpartum knockout females had enlarged, fibrotic hearts, decreased vascular density in the heart and other signs of cardiomyopathy.

Additional experiments in the knockout mice confirmed that lack of *Pgc-1 α* downregulated two proangiogenic pathways in the heart to cause PPCM. These findings led the group to speculate that human PPCM might also result from an angiogenic deficiency.

The researchers suspected the culprit was a soluble form of VEGF receptor 1 (FLT1; VEGFR-1). Soluble FLT1 (sFLT1) is an antiangiogenic factor normally secreted by the placenta in late pregnancy, resulting in increased serum levels during the peripartum period. However, the levels are much greater in peripartum women with preeclampsia than in healthy peripartum women.²

In healthy and most preeclamptic peripartum women, serum levels of sFLT1 return to normal, prepregnancy levels within three days after delivery.

The team found that at 4–6 weeks after delivery, sFLT1 levels were 5- to 10-fold higher

in women who had preeclampsia and PPCM than in postpartum women who did not have either condition.

Next, the team showed that in prepartum women with preeclampsia, higher sFLT1 correlated with lower cardiac function as measured by echocardiography. Similar cardiac dysfunction, cardiomyopathy and heart failure occurred when murine sFLT1 was given to pregnant wild-type mice, nonpregnant wild-type mice and nonpregnant cardiac-specific *Pgc-1 α* knockout mice.

Data were reported in *Nature*.¹

Collectively, the findings suggest increased levels of sFLT1 cause

(Continues on p. 6)

“We also think—but don’t know yet—that the mechanism we describe in this study will apply to all cases of PPCM, not just the one-third associated with preeclampsia.”

—Zoltan Arany,
Harvard Medical School

(Continued from “Cooling down AD,” p. 4)

testing. Her challenge is to improve the drug’s efficacy. Her team’s preclinical work showed that increasing the dose of the drug actually worsened cognitive performance.

“One possibility is that the drug is directly suppressing A β levels, but there is no evidence for that yet.”

—John Cirrito,
Washington University in St. Louis

She does think the modest effect of the drug on functional performance could be improved by longer dosing. Gallagher suspects that chronic treatment with low doses

of levetiracetam might lead to sustained functional improvement and might even slow the progression of MCI into AD.

AgeneBio plans to advance an undisclosed compound that is related to levetiracetam into a Phase II trial in patients with MCI. The company did not disclose when that trial would begin. AgeneBio also

has a compound that targets GABA_A receptor, another epilepsy target, in preclinical development for AD.

Osheroich, L. *SciBX* 5(21); doi:10.1038/scibx.2012.537
Published online May 24, 2012

REFERENCES

- Bakker, A. *et al. Neuron*; published online May 10, 2012; doi:10.1016/j.neuron.2012.03.023
Contact: Michela Gallagher, The Johns Hopkins University, Baltimore, Md.
e-mail: michela@jhu.edu
- Wilson, I.A. *et al. J. Neurosci.* **25**, 6877–6886 (2005)
- Minkeviciene, R. *et al. J. Neurosci.* **29**, 3453–3462 (2009)

COMPANIES AND INSTITUTIONS MENTIONED

AgeneBio Inc., Carmel, Ind.
Gladstone Institute of Neurological Disease, San Francisco, Calif.
The Johns Hopkins University, Baltimore, Md.
UCB Group (Euronext:UCB), Brussels, Belgium
University of California, San Francisco, Calif.
Washington University in St. Louis, St. Louis, Mo.

Getting selective for γ

By *Tim Fulmer, Senior Writer*

Cellzome AG and **Exelixis Inc.** have independently designed the first highly selective inhibitors of the γ -isoform of phosphoinositide 3-kinase.^{1,2} Exelixis plans to out-license its inhibitors, whereas last week's acquisition of Cellzome by **GlaxoSmithKline plc** gives the pharma a new class of compounds for inflammatory and autoimmune diseases.

Phosphoinositide 3-kinase (PI3K) plays a central role in signaling pathways that contribute to cell growth, proliferation, motility and survival. The kinase occurs in four isoforms. The α - and β -isoforms are expressed in many tissues and cell types, and the γ - and δ -isoforms

are expressed in immune cells.

Aberrant activation of PI3K α and PI3K β is a key driver of many solid cancers, whereas activation of PI3K γ and PI3K δ can lead to hematological malignancies and inflammatory diseases.

For the past decade, the challenge has been to design PI3K inhibitors that selectively hit the isoform implicated in a given disease while sparing the function of the other isoforms. That has generally required chemists to optimize inhibitors that are 10–1,000 times more selective for one isoform over the others.³

Selective inhibitors of PI3K α and PI3K δ have moved into the clinic, and inhibitors of PI3K β are in preclinical testing (*see Table 1, "PI3K γ and PI3K δ inhibitor pipeline"*). Inhibiting PI3K γ has been more difficult.

(Continues on p. 7)

(Continued from "Getting around peripartum cardiomyopathy," p. 5)

PPCM that is associated with preeclampsia. The results also suggest that lowering sFLT1 levels could help treat PPCM, team leader Zoltan Arany told *SciBX*.

"We also think—but don't know yet—that the mechanism we describe in this study will apply to all cases of PPCM, not just the one-third associated with preeclampsia," he said.

Arany is assistant professor of medicine at HMS and a principal investigator at **Beth Israel Deaconess Medical Center**. The team included researchers from the **Howard Hughes Medical Institute (HHMI)** and **Hannover Medical School**.

Flt to be tried

Going forward, the challenges are identifying feasible sFLT1-reducing strategies and determining whether increased sFLT1 plays a causal role in the broader population of patients with PPCM.

Arany noted that last year, a group from HMS and **Massachusetts General Hospital** reported results from a pilot study showing that a dialysis-like device that removed circulating sFLT1 was successful in treating preeclampsia.³

That group was led by S. Ananth Karumanchi, coauthor on the current *Nature* study. Karumanchi is an associate professor of medicine at HMS, senior scientist at Beth Israel and investigator at HHMI.

"In theory, his device could also be used to treat PPCM," Arany said. "But another, less cumbersome way to treat the disease would be to use a systemic small molecule to inhibit sFLT1 secretion."

Arany's team is now looking for such molecules. He said FLT1 inhibitors on the market to treat renal cancer and/or sarcoma—such as Votrient pazopanib from **GlaxoSmithKline plc** and Inlyta axitinib from **Pfizer Inc.**—are unlikely to be suitable for the PPCM indication. Those molecules, he noted, are intended to block activity of membrane-bound FLT1 as opposed to neutralizing the circulating, soluble form of the receptor.

sFLT1 is thought to play an important prepartum role by disconnecting the link between the mother's and baby's vascular systems—thereby protecting the mother from potentially fatal blood loss during childbirth. However, Arany does not think lowering sFLT1 to treat PPCM would raise major safety concerns because the indication is diagnosed after delivery.

He added that the source of increased postpartum sFLT1 is unknown

but is thought to come from placental remnants, syncytial microparticles shed by the placenta or circulating mononuclear cells able to express the protein.

In addition to identifying inhibitors of sFLT1 secretion, Arany said the group is conducting serial blood tests and other prospective studies in pregnant women to investigate whether sFLT1 could be a marker or a therapeutic target in cases of PPCM not associated with preeclampsia.

Earlier this year, a team led by Karumanchi reported that sFLT1 could be a diagnostic and prognostic marker for preeclampsia.⁴ Current markers for the condition are high blood pressure and protein in the urine, but they do not predict outcomes.

If prepartum sFLT1 also proves to be a risk marker for PPCM, sFLT1-reducing therapy might be used to prevent the disease, Arany said. "I think prevention in high-risk, prepartum women is a good approach and might even be better than treatment," he said.

Arany added that the caveat is that a prophylactic would have to reduce sFLT1 levels only to what is normal in prepartum women.

The findings reported in *Nature* are not patented and are available for partnering, Arany said.

Haas, M.J. *SciBX* 5(21); doi:10.1038/scibx.2012.538
Published online May 24, 2012

REFERENCES

- Patten, I.S. *et al. Nature*; published online May 9, 2012; doi:10.1038/nature11040
Contact: Zoltan Arany, Harvard Medical School, Boston, Mass.
e-mail: zarany@bidmc.harvard.edu
Contact: Denise Hilfiker-Kleiner, Hannover Medical School, Hannover, Germany
e-mail: hilfiker.denise@mh-hannover.de
- Levine, R.J. *et al. N. Engl. J. Med.* **350**, 672–683 (2004)
- Thadhani, R. *et al. Circulation* **124**, 940–950 (2011)
- Rana, S. *et al. Circulation* **125**, 911–919 (2012)

COMPANIES AND INSTITUTIONS MENTIONED

Beth Israel Deaconess Medical Center, Boston, Mass.
GlaxoSmithKline plc (LSE:GSK; NYSE:GSK), London, U.K.
Hannover Medical School, Hannover, Germany
Harvard Medical School, Boston, Mass.
Howard Hughes Medical Institute, Chevy Chase, Md.
Massachusetts General Hospital, Boston, Mass.
Pfizer Inc. (NYSE:PFE), New York, N.Y.

Genetic data from a variety of animal models suggest selectively inhibiting PI3K γ could have a broad anti-inflammatory effect with potential utility in a range of diseases,⁴ including rheumatoid arthritis (RA),⁵ atherosclerosis⁶ and diabetes.^{7,8} Highly selective inhibition of PI3K γ also should avoid the cardiotoxicity that has been associated with some PI3K inhibitors in mice that antagonize the PI3K α isoform (see Box 1, “Heartless PI3K inhibition”).

Chemical scaffolds that work for the other three isoforms “often fail to potently inhibit PI3K γ ,” Christian Rommel told *SciBX*. “The ATP-binding pocket of PI3K γ is structurally distinct [from the other isoforms] and is more tight and narrow as well as less flexible.”

Rommel is the former CSO of Intellikine Inc., which was acquired by **Takeda Pharmaceutical Co. Ltd.** this year for \$190 million up front and up to \$120 million in milestones. While at Intellikine, Rommel oversaw the development of INK1117, a PI3K α -selective PI3K inhibitor that is in Phase I testing to treat solid tumors, and IPI-145, a dual inhibitor of PI3K γ and PI3K δ that is in Phase I testing to treat hematological malignancies.

Compared with dual inhibition of PI3K γ and PI3K δ , inhibiting only PI3K γ “is thought to be more suitable for myeloid-triggered inflammatory processes implicated in atherosclerosis and certain forms of metabolic disorders,” said Rommel.

Going native

Cellzome researchers reasoned they might have a better chance of identifying a PI3K γ -selective PI3K inhibitor by using initial compound screens in whole-cell extracts rather than in panels of purified recombinant kinases.

The goal was to test the activity of inhibitors in a setting that mimics physiology, VP of Research Operations Gitte Neubauer told *SciBX*.

“The targets are full length, post-translationally modified, and their interactions with other proteins are largely preserved,” she said.

“There has been a growing realization that recombinant protein kinases, which are often truncated and/or fusion proteins, do not exhibit the same activity and drug-binding properties as kinases in native cells and tissues,” said Matthew Patricelli, director of technology at **ActivX Biosciences Inc.**

“There has been a growing realization that recombinant protein kinases, which are often truncated and/or fusion proteins, do not exhibit the same activity and drug-binding properties as kinases in native cells and tissues.”

—Matthew Patricelli,
ActivX Biosciences Inc.

Biosciences Inc.

Proteome-wide analysis of compound selectivity against native kinases in the presence of cellular cofactors “is particularly useful to inform decisions, for example, in the lead optimization phase or in the clinical candidate selection process,” said Henrik Daub, SVP of science and technology at **Evotec AG**.

ActivX’s KiNativ platform and Evotec’s Kinaxo platform both allow for proteome-wide kinase inhibitor profiling in cell and tissue extracts.^{9,10}

To identify molecules that could serve as starting points for optimization of highly selective inhibitors of PI3K γ , Cellzome used its Kinobeads chemical proteomics platform.

The platform uses a resin matrix coated with immobilized analogs of small molecules that broadly bind kinases. The resin is incubated in a fresh cell extract along with a test compound or vehicle.

The arrangement sets up a competitive binding assay in which the test compound competes with the resin to bind PI3K γ in the cell extract. Hits are then identified by reduced binding of PI3K γ to the resin, which indicates the test compound binds PI3K γ more strongly than the resin and thus could be the starting point for inhibitor optimization.

Previously, the researchers had validated the platform by confirming its ability to predict the known targets of a panel of multikinase inhibitors, including the cancer drugs Gleevec imatinib from **Novartis AG** and Sprycel dasatinib from **Bristol-Myers Squibb Co.**¹¹

Table 1. PI3K γ and PI3K δ inhibitor pipeline. There are at least six companies developing inhibitors that are selective for phosphoinositide 3-kinase- δ (PI3K δ) or selective for both PI3K γ and PI3K δ . Hematological malignancies and inflammation are the main indications being pursued. The IC₅₀ value indicates the concentration of compound needed to inhibit PI3K signaling by 50% and serves as a rough measure of the relative selectivity of an inhibitor for one isoform over another. Lower IC₅₀ values generally indicate greater potency.

Source: *BCIQ: BioCentury Online Intelligence. Shuttleworth, S.J. et al. Curr. Med. Chem.* **18**, 2686–2714 (2011)

Company	Compound	Intended target(s)	Isoform selectivity IC ₅₀ value (nM)	Lead indication(s)	Status
Gilead Sciences Inc. (NASDAQ:GILD)	GS-1101	PI3K δ	PI3K α : >100,000 PI3K β : 1,820 PI3K γ : 1,240 PI3K δ : 70	Chronic lymphocytic leukemia (CLL); non-Hodgkin's lymphoma (NHL)	Phase III
Amgen Inc. (NASDAQ:AMGN)	AMG 319	PI3K δ	Not available	Hematologic malignancies	Phase I
Takeda Pharmaceutical Co. Ltd. (Tokyo:4502)/ Infinity Pharmaceuticals Inc. (NASDAQ:INFI)/ Mundipharma International Ltd.	IPI-145	PI3K δ and PI3K γ	Not available	Hematologic malignancies; autoimmune disorders	Phase I
Exelixis Inc. (NASDAQ:EXEL)/ Merck & Co. Inc. (NYSE:MRK)	XL499	PI3K δ	Not available	Allergic asthma; inflammation	Preclinical
Karus Therapeutics Ltd.	KAR4139	PI3K δ and PI3K β	Not available	Cancer; inflammation	Preclinical
	KAR4141	PI3K δ	Not available	Inflammation	Preclinical
Pathway Therapeutics Inc.	PI3K δ	PI3K δ	≥100 times more selective over PI3K α , PI3K β and PI3K γ	Hematologic malignancies; inflammation; respiratory disorders	Preclinical

Box 1. Heartless PI3K inhibition.

A study published in *Science Translational Medicine* by researchers from the **State University of New York at Stony Brook** showed that blocking phosphoinositide 3-kinase- α (PI3K α) signaling in the heart triggered prolongation of the QT interval in mice and in cultured canine ventricular myocytes.¹²

In mice, cardiac-specific knockout of PI3K α led to increased action potential duration (APD) compared with that seen in wild-type animals, whereas cardiac-specific knockout of PI3K β had minimal effects on APD. When the PI3K β knockout mice were treated with a PI3K α inhibitor, the animals showed APD length comparable to that in the PI3K α knockout mice.

Moreover, echocardiogram (ECG) readings of hearts isolated from the PI3K α knockout mice showed the QT interval was almost twice as long as that in wild-type controls. In cultured canine myocytes, **Novartis AG's** PI3K α and mammalian target of rapamycin (mTOR; FRAP; RAFT1) dual inhibitor, BEZ235, increased APD compared with vehicle.

Those results suggest that in the mouse heart, reduced signaling by the PI3K α isoform solely mediates APD prolongation.

The authors concluded that patients treated with PI3K inhibitors and other drugs targeting PI3K signaling in the heart “should be closely monitored for QT prolongation and cardiac arrhythmias.”

Corresponding author Richard Lin told *SciBX* that he and corresponding author Ira Cohen “are actively investigating how to counter the off-target proarrhythmic effect caused by PI3K inhibitors and other drugs that inhibit PI3K signaling.” He declined to provide additional details.

Lin and Cohen are professors of physiology and biophysics at SUNY Stony Brook. Cohen also is director of the university's Institute of Molecular Cardiology.

Both PI3K α -selective inhibitors and PI3K α and mTOR dual inhibitors are in the clinic.

PI3K α -selective inhibitors include GDC-0941 from **Roche**, which is in Phase II testing for breast cancer, and BYL719 from Novartis and INK1117 from **Takeda Pharmaceutical Co. Ltd.**, both of which are in Phase I testing for solid tumors.

PI3K α and mTOR dual inhibitors include BEZ235 from Novartis, which is in Phase I/II testing for solid cancers; XL765 from **Exelixis Inc.** and **Sanofi**, which is in Phase Ib/II testing for gliomas and solid tumors; and PWT33597 from **Pathway Therapeutics Inc.**, which is in Phase I testing for solid tumors.

None of the companies responded to requests for comment.

However, data presented at the 2009 and 2010 American Society of Clinical Oncology and American Association of Cancer Research meetings showed that BEZ235 had no dose-limiting toxicities and had mild adverse events including nausea, diarrhea and anemia. XL765 also showed good tolerability with adverse events similar to those of BEZ235.¹³

—TF

In the new work, the team modified the resin to bind PI3K γ as well as potential off-target kinases PI3K δ , mammalian target of rapamycin (mTOR; FRAP; RAFT1) and DNA-dependent protein kinase (DNA-PK), and then they screened a library of 16,146 small molecules for selective inhibition of PI3K γ .

The lead hit of that screen, CZC19091, was potent and at least 20 times more selective for PI3K γ over the off-target kinases. However, the compound was poorly active in cellular assays and showed poor exposure in rats.

The researchers then made three chemical modifications to CZC19091, which led to the highly selective PI3K γ inhibitor CZC24832. The compound was more potent than the parent molecule. CZC24832 also was 100 times more selective for PI3K γ over PI3K α and PI3K δ and 30 times more selective over PI3K β . The compound showed strong activity in cellular assays and good exposure in rats.

In a mouse model of collagen-induced arthritis, CZC24832 decreased bone and cartilage destruction by 53% compared with vehicle control, confirming the compound's anti-inflammatory activity.

Finally, the team used the inhibitor to uncover a new role for PI3K γ in the regulation of proinflammatory T cells. In a panel of human primary cell co-cultures exposed to inflammatory stimuli, CZC24832 inhibited RAR-related orphan receptor C thymus-specific isoform (ROR γ 2; ROR γ T) expression, blocking differentiation of naive T cells into T helper type 17 (Th17) cells and reducing the number of IL-17-producing cells.

“Our results revealed a previously undescribed role of PI3K γ in the regulation of T_H17 differentiation, supporting the involvement of PI3K γ in the control of both innate and adaptive immune mechanisms,” the authors wrote in their paper in *Nature Chemical Biology*.

Although the lead PI3K γ inhibitor identified in the *Nature Chemical Biology* paper “is a very good and selective *in vivo* probe compound, it does not have ideal physical-chemical properties. Further optimization would be needed before it might be considered a clinical candidate,” Neubauer said. She declined to provide additional details, and GSK did not respond to requests for comment.

For obesity-related diseases, “it will be important to evaluate the toxicity of CZC24832 following chronic, *in vivo* administration in the relevant animal models,” said Giovanni Solinas, professor of physiology and medicine at the **University of Fribourg**.

Solinas and colleagues have shown that PI3K γ promotes obesity and insulin resistance in mice on a high-fat diet.⁷

Cellzome and GSK have been working together since 2008 to discover and develop kinase-targeted therapeutics using the Kinobeads platform, and GSK had an exclusive option to license any product candidates.

Neubauer declined to disclose if any compounds that have been discovered under that deal target PI3K γ or other PI3K isoforms.

Back to basics

Exelixis opted for a different approach than Cellzome and stuck with the standard structure-based design methods Exelixis used to discover and optimize selective inhibitors of PI3K α , PI3K β and PI3K δ .

“We had two key things working in our favor that made us believe we could use a traditional structure-based design approach” to discover PI3K γ inhibitors, Exelixis CSO and EVP of discovery research Peter Lamb told *SciBX*. “First, we have a very large in-house screening library

of about 4.5 million compounds that includes a broad range of scaffolds and chemotypes. Second, we have X-ray crystal structures of PI3K γ bound to some of those chemotypes, which, we believed, could inform

“Based on the data we’ve gathered so far, we believe PI3K γ inhibitors have broad-spectrum anti-inflammatory activity and could find therapeutic uses in autoimmune indications like rheumatoid arthritis, multiple sclerosis and lupus, as well as in airway inflammation diseases such as asthma and COPD [chronic obstructive pulmonary disease].”

—Peter Lamb, Exelixis Inc.

and guide our optimization of inhibitors that would be at least 10 times more selective for PI3K γ over the other isoforms.”

An *in vitro* high throughput screen of the company’s entire compound library revealed two hits that, with subsequent optimization, generated a series of about 30 small molecules that bound PI3K γ with varying levels of potency and selectivity.

The four most potent and selective inhibitors had PI3K γ IC₅₀ values of 5, 8, 18 and 34 nM and were all 10–500 times more

selective for PI3K γ over the other isoforms. The compounds also had good plasma exposure in mice and rats.

In a mouse model of inflammation-associated mast cell degranulation, all four compounds decreased degranulation compared with vehicle and did so at levels comparable to those seen in PI3K γ knockout mice.

Finally, in a mouse model of chemokine-induced proinflammatory neutrophil recruitment, the 34 nM inhibitor lowered recruitment by 50% compared with vehicle ($p < 0.05$).

Results were published in the *Journal of Medicinal Chemistry*.

“Based on the data we’ve gathered so far, we believe PI3K γ inhibitors have broad-spectrum anti-inflammatory activity and could find therapeutic uses in autoimmune indications like rheumatoid arthritis, multiple sclerosis and lupus, as well as in airway inflammation diseases such as asthma and COPD [chronic obstructive pulmonary disease],” said Lamb.

Exelixis wants to partner its PI3K γ inhibitor program. “We are not actively working on this program now, as almost all of the company’s resources are focused on our lead cancer compound, cabozantinib,” he said.

Cabozantinib (XL184), an inhibitor of c-Met receptor tyrosine kinase (MET; HGFR) and VEGF signaling, is in a Phase III trial to treat medullary thyroid cancer and in two Phase II trials to treat a broad

range of solid cancers. Next month the company will present data on the trials at the annual American Society of Clinical Oncology meeting in Chicago.

Exelixis also is interested in licensing its preclinical PI3K α inhibitor program, said Lamb. Earlier this year, the company exclusively licensed its preclinical PI3K δ program to **Merck & Co. Inc.**

The PI3K γ inhibitors in both papers are covered by patents.

Fulmer, T. *SciBX* 5(21); doi:10.1038/scibx.2012.539

Published online May 24, 2012

REFERENCES

- Bergamini, G. *et al. Nat. Chem. Biol.*; published online April 29, 2012; doi:10.1038/nchembio.957
Contact: Gitte Neubauer, Cellzome AG, Heidelberg, Germany
e-mail: gitte.neubauer@cellzome.com
Contact: Marcus Bantscheff, same affiliation as above
e-mail: marcus.bantscheff@cellzome.com
- Leahy, J.W. *et al. J. Med. Chem.*; published online May 1, 2012; doi:10.1021/jm300403a
Contact: Henry W.B. Johnson, Exelixis Inc., South San Francisco, Calif.
e-mail: hjohnson@exelixis.com
- Fulmer, T. *BioCentury* 20(9), A9–A13; Feb. 27, 2012
- Rückle, T. *et al. Nat. Rev. Drug Discov.* 5, 903–918 (2006)
- Rommel, C. *et al. Nat. Rev. Immunol.* 7, 191–201 (2007)
- Fougerat, A. *et al. Circulation* 117, 1310–1317 (2008)
- Becattini, B. *et al. Proc. Natl. Acad. Sci. USA* 108, E854–E863 (2011)
- Kobayashi, N. *et al. Proc. Natl. Acad. Sci. USA* 108, 5753–5758 (2011)
- Sharma, K. *et al. Nat. Methods* 6, 741–744 (2009)
- Patricelli, M.P. *et al. Chem. Biol.* 18, 699–710 (2011)
- Bantscheff, M. *et al. Nat. Biotechnol.* 25, 1035–1044 (2007)
- Lu, Z. *et al. Sci. Transl. Med.*; published online April 25, 2012; doi:10.1126/scitranslmed.3003623
Contact: Ira S. Cohen, State University of New York at Stony Brook, Stony Brook, N.Y.
e-mail: ira.cohen@stonybrook.edu
Contact: Richard Z. Lin, same affiliation as above
e-mail: richard.lin@stonybrook.edu
- Wander, S.A. *et al. J. Clin. Invest.* 121, 1231–1241 (2011)

COMPANIES AND INSTITUTIONS MENTIONED

ActivX Biosciences Inc., La Jolla, Calif.
Bristol-Myers Squibb Co. (NYSE: BMY), New York, N.Y.
Cellzome AG, Heidelberg, Germany
Evotec AG (Xetra:EVT), Hamburg, Germany
Exelixis Inc. (NASDAQ: EXEL), South San Francisco, Calif.
GlaxoSmithKline plc (LSE: GSK; NYSE: GSK), London, U.K.
Merck & Co. Inc. (NYSE: MRK), Whitehouse Station, N.J.
Novartis AG (NYSE: NVS; SIX: NOVN), Basel, Switzerland
Pathway Therapeutics Inc., San Francisco, Calif.
Roche (SIX: ROG; OTCQX: RHHBY), Basel, Switzerland
Sanofi (Euronext: SAN; NYSE: SNY), Paris, France
State University of New York at Stony Brook, Stony Brook, N.Y.
Takeda Pharmaceutical Co. Ltd. (Tokyo: 4502), Osaka, Japan
University of Fribourg, Fribourg, Switzerland

This week in therapeutics

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

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

Indication	Target/marker/pathway	Summary	Licensing status	Publication and contact information
Cancer				
Brain cancer	BRAF; cyclin dependent kinase inhibitor 2A (CDKN2A; INK4a; ARF; p16INK4a); cyclin dependent kinase 4 (CDK4); CDK6	<p>Mouse studies suggest a BRAF inhibitor plus a CDK4 and CDK6 inhibitor could help treat pediatric astrocytomas that carry the BRAF V600E mutation and have a CDKN2A deficiency. In a mouse xenograft model of BRAF V600E-mutant and CDKN2A-deficient human astrocytoma, Zelboraf vemurafenib plus the CDK4 and CDK6 inhibitor PD-0332991 increased survival compared with either compound alone ($p=0.0018$). Next steps include evaluating Zelboraf and PD-0332991 as monotherapies in a Phase I trial in pediatric glioma before testing the combination.</p> <p>Zelboraf, an oral small molecule inhibitor of oncogenic BRAF V600E from Daiichi Sankyo Co. Ltd., Chugai Pharmaceutical Co. Ltd. and Roche, is marketed to treat melanoma. The drug also is in Phase II testing to treat thyroid cancer and Phase I testing to treat colorectal cancer.</p> <p>PD-0332991 from Onyx Pharmaceuticals Inc. and Pfizer Inc. is in Phase II testing to treat cancer.</p> <p>SciBX 5(21); doi:10.1038/scibx.2012.540 Published online May 24, 2012</p>	Patented for use in melanoma; licensing status undisclosed	<p>Huillard, E. <i>et al. Proc. Natl. Acad. Sci. USA</i>; published online May 14, 2012; doi:10.1073/pnas.1117255109</p> <p>Contact: David H. Rowitch, University of California, San Francisco, Calif. e-mail: rowitchd@peds.ucsf.edu</p> <p>Contact: C. David James, same affiliation as above e-mail: david.james@ucsf.edu</p>
Cancer	DNA	<p>Mouse and cell culture studies identified mithramycin analogs that could help treat cancer. In a panel of 60 human cancer cell lines, the 2 most potent analogs caused 50% growth inhibition at average concentrations of 30 and 28 nM. In mouse xenograft models of human melanoma and colorectal cancer, the lead analog caused stronger tumor growth inhibition than cisplatin. Spinoff company EntreChem S.L. is carrying out toxicity and efficacy studies in animals.</p> <p>SciBX 5(21); doi:10.1038/scibx.2012.541 Published online May 24, 2012</p>	Mithramycin analogs patented; available for licensing from EntreChem	<p>Núñez, L.E. <i>et al. J. Med. Chem.</i>; published online May 14, 2012; doi:10.1021/jm300234t</p> <p>Contact: Carmen Méndez, University of Oviedo, Oviedo, Spain e-mail: cmendezf@uniovi.es</p>
Cancer	K-Ras; son of sevenless homolog 1 (SOS1)	<p>Two independent <i>in vitro</i> studies identified a previously unknown binding site on K-Ras that could be targeted with small molecules to treat cancer. <i>In vitro</i> screening of libraries made up of small molecule fragments identified ligands that bound to a site at the likely interface of K-Ras and its activator SOS1. In an <i>in vitro</i> assay, fragments or fragment analogs blocked SOS1-mediated K-Ras activation with mid- to high-micromolar IC_{50} values. Next steps for both groups include developing more potent inhibitors (<i>see Reviving Ras</i>, page 1).</p> <p>SciBX 5(21); doi:10.1038/scibx.2012.542 Published online May 24, 2012</p>	<p>Patent status undisclosed for first study; available for licensing or partnering</p> <p>Patent status undisclosed for second study; unavailable for licensing</p>	<p>Sun, Q. <i>et al. Angew. Chem. Int. Ed.</i>; published online May 8, 2012; doi:10.1002/anie.201201358</p> <p>Contact: Stephen W. Fesik, Vanderbilt University School of Medicine, Nashville, Tenn. e-mail: stephen.fesik@vanderbilt.edu</p> <p>Maurer, T. <i>et al. Proc. Natl. Acad. Sci. USA</i>; published online March 19, 2012; doi:10.1073/pnas.1116510109</p> <p>Contact: Guowei Fang, Genentech Inc., South San Francisco, Calif. e-mail: fang.guowei@gene.com</p> <p>Contact: Weiru Wang, same affiliation as above e-mail: wang.weiru@gene.com</p>

This week in therapeutics (continued)

Indication	Target/marker/ pathway	Summary	Licensing status	Publication and contact information
Cancer	P glycoprotein (MDR1; ABCB1; P-gp; CD243)	Cell culture studies identified ecdysteroid compounds that could help treat multidrug-resistant (MDR) cancers. In a mouse lymphoma cell line overexpressing Abcb1, multiple ecdysteroids decreased resistance to doxorubicin compared with no treatment. Next steps include evaluating the lead ecdysteroids against additional cell lines with other resistance mechanisms and in non-MDR cell lines. Hanmi Pharmaceutical Co. Ltd.'s Oraxol, an oral formulation of paclitaxel plus an ABCB1 inhibitor, is in Phase II testing to treat cancer. The company's Oratecan, an oral formulation of irinotecan plus an ABCB1 inhibitor, is in Phase I testing for cancer. SciBX 5(21); doi:10.1038/scibx.2012.543 Published online May 24, 2012	Unpatented; licensing status not applicable	Martins, A. <i>et al. J. Med. Chem.</i> ; published online May 14, 2012; doi:10.1021/jm300424n Contact: Attila Hunyadi, University of Szeged, Szeged, Hungary e-mail: hunyadi.a@pharm.u-szeged.hu
Cancer	p21 Protein (Cdc42 Rac)-activated kinase 4 (PAK4)	<i>In vitro</i> and rodent studies identified a pyrroloaminopyrazole series of PAK4 inhibitors that could help treat cancers. Alkyl amides from the series had potent activity against the kinase <i>in vitro</i> and had favorable oral bioavailability in rats. In mice with human melanoma and colon cancer PAK4-driven xenografts, two of the compounds decreased tumor volume compared with no treatment. Next steps could include testing the inhibitors in additional animal models. SciBX 5(21); doi:10.1038/scibx.2012.544 Published online May 24, 2012	Patent and licensing status unavailable	Guo, C. <i>et al. J. Med. Chem.</i> ; published online May 3, 2012; doi:10.1021/jm300204j Contact: Chuangxing Guo, Pfizer Global Research and Development, San Diego, Calif. e-mail: alexguo01@gmail.com Contact: Indrawan McAlpine, same affiliation as above e-mail: indrawan.mcalpine@pfizer.com
Cancer	Sirtuin 7 (SIRT7)	<i>In vitro</i> and mouse studies suggest inhibiting SIRT7 could help treat cancer. <i>In vitro</i> studies identified SIRT7 as an H3K18-specific deacetylase and showed that SIRT7-targeting small interfering RNA inhibited cancer-associated properties. In mice injected with transformed cancer cell lines, SIRT7 siRNA pretreatment decreased tumor growth compared with control siRNA pretreatment. Next steps include determining whether SIRT7 is involved in the oncogenic transformation of noncancerous cells. SciBX 5(21); doi:10.1038/scibx.2012.545 Published online May 24, 2012	Unpatented; licensing status not applicable	Barber, M.F. <i>et al. Nature</i> ; published online May 6, 2012; doi:10.1038/nature11043 Contact: Katrin F. Chua, Stanford University, Stanford, Calif. e-mail: kfchua@stanford.edu Contact: Wei Li, Baylor College of Medicine, Houston, Texas e-mail: w11@bcm.edu
Cancer	Topoisomerase I (TOP1); tyrosyl-DNA phosphodiesterase 1 (TDP1)	<i>In vitro</i> studies identified a <i>bis</i> (indenoisoquinoline)-based inhibitor of TOP1 and TDP1 that could help treat cancer. <i>In vitro</i> , the most potent molecule inhibited human TDP1 with an IC ₅₀ of 1.9 μM and also inhibited TOP1 with potency comparable to that of the TOP1 inhibitor camptothecin. Next steps could include optimizing the compound and evaluating it in animal cancer models. Camptosar irinotecan, a semisynthetic derivative of camptothecin, is marketed by Yakult Honsha Co. Ltd. and Pfizer Inc. to treat colorectal and non-small cell lung cancers. At least 10 other companies have camptothecin analogs and derivatives in Phase III trials or earlier to treat cancer. SciBX 5(21); doi:10.1038/scibx.2012.546 Published online May 24, 2012	Patent and licensing status unavailable	Nguyen, T.X. <i>et al. J. Med. Chem.</i> ; published online April 26, 2012; doi:10.1021/jm300335n Contact: Mark Cushman, Purdue University, West Lafayette, Ind. e-mail: cushman@purdue.edu

This week in therapeutics (continued)

Indication	Target/marker/pathway	Summary	Licensing status	Publication and contact information
Melanoma	Phosphatidylinositol-3,4,5-triphosphate-dependent Rac exchange factor 2 (PREX2)	Genomic and mouse studies identified PREX2 mutants in melanomas that could be inhibited to help treat the cancer. Genomic sequencing identified <i>PREX2</i> mutations in tumor tissue from 14% of 107 patients with melanoma. In mice, transplantation of melanoma cell lines expressing mutant <i>PREX2</i> led to greater tumorigenesis than transplantation of cells expressing wild-type <i>PREX2</i> . Next steps include additional mechanistic studies to determine the role of PREX2 in tumorigenesis. SciBX 5(21); doi:10.1038/scibx.2012.547 Published online May 24, 2012	Unpatented; licensing status not applicable	Berger, M.F. <i>et al. Nature</i> ; published online May 9, 2012; doi:10.1038/nature11071 Contact: Levi A. Garraway, Broad Institute of MIT and Harvard, Cambridge, Mass. e-mail: levi_garraway@dfci.harvard.edu Contact: Lynda Chin, The University of Texas MD Anderson Cancer Center, Houston, Texas e-mail: lchin@mdanderson.org
Prostate cancer	Tyrosine kinase non-receptor 2 (Tnk2; ACK1)	Mouse and cell culture studies suggest inhibiting ACK1 could help reverse resistance to radiotherapy in castration-resistant prostate cancer (CRPC). In a mouse model of radiation-resistant CRPC, an inhibitor of ACK1 restored sensitivity to radiation therapy. Next steps include developing optimized ACK1 inhibitors and evaluating them in radiotherapy-resistant CRPC. SciBX 5(21); doi:10.1038/scibx.2012.548 Published online May 24, 2012	Unpatented; available for collaboration	Mahajan, K. <i>et al. J. Biol. Chem.</i> ; published online May 7, 2012; doi:10.1074/jbc.M112.357384 Contact: Nupam P. Mahajan, H. Lee Moffitt Cancer Center & Research Institute, Tampa, Fla. e-mail: nupam.mahajan@moffitt.org
Skin cancer	Survivin (BIRC5)	Mouse studies suggest survivin inhibitors could help treat Merkel cell carcinoma, a form of skin cancer caused by the Merkel cell polyomavirus. In a mouse xenograft model of Merkel cell carcinoma, the small molecule survivin inhibitor YM155 delayed tumor growth and increased survival compared with the proteasome inhibitor Velcade bortezomib or saline ($p < 0.0001$ for both). Next steps include evaluating a survivin inhibitor in a Phase I/II trial. Astellas Pharma Inc.'s YM155 is in Phase II testing for breast cancer, melanoma and non-Hodgkin's lymphoma. At least eight other companies have survivin inhibitors in Phase II testing or earlier to treat cancer. Takeda Pharmaceutical Co. Ltd. and Johnson & Johnson market Velcade to treat multiple myeloma (MM) and mantle cell lymphoma (MCL). SciBX 5(21); doi:10.1038/scibx.2012.549 Published online May 24, 2012	Patents pending; available for licensing from the University of Pittsburgh Contact: Alexander Ducruet, University of Pittsburgh, Pittsburgh, Pa. e-mail: apdst11@pitt.edu	Arora, R. <i>et al. Sci. Transl. Med.</i> ; published online May 9, 2012; doi:10.1126/scitranslmed.3003713 Contact: Patrick S. Moore, University of Pittsburgh, Pittsburgh, Pa. e-mail: psm9@pitt.edu Contact: Yuan Chang, same affiliation as above e-mail: yc70@pitt.edu
Solid tumors	NAD(P)H dehydrogenase quinone 1 (NQO1; QR1)	<i>In vitro</i> and mouse studies identified deoxyxyboquinone (DNQ) as a new NQO1 substrate that could help treat solid tumors. In human breast cancer and non-small cell lung cancer (NSCLC) cell lines expressing the redox enzyme NQO1, DNQ induced more cell death than the NQO1-targeting compound β -lapachone. In the cancer cell lines, DNQ induced lethality in NQO1-expressing cells but not in NQO1-deficient cells. In a mouse Lewis lung carcinoma model, DNQ decreased tumor growth with similar potency but at a six-fold lower dose than β -lapachone. Next steps include developing DNQ analogs with better stability. Edison Pharmaceuticals Inc.'s EPI-743, an oral small molecule targeting NQO1, is in Phase II/III testing to treat mitochondrial disease. SciBX 5(21); doi:10.1038/scibx.2012.550 Published online May 24, 2012	Patents filed; in negotiations to license technology to StemPAR Sciences Inc., which has already licensed β -lapachone	Huang, X. <i>et al. Cancer Res.</i> ; published online April 24, 2012; doi:10.1158/0008-5472.CAN-11-3135 Contact: David A. Boothman, The University of Texas Southwestern Medical Center, Dallas, Texas e-mail: david.boothman@utsouthwestern.edu

This week in therapeutics (continued)

Indication	Target/marker/pathway	Summary	Licensing status	Publication and contact information
Cardiovascular disease				
Thrombosis	Protein disulfide isomerase (PDI)	<i>In vitro</i> and mouse studies identified a PDI inhibitor that could help prevent thrombosis. In cellular assays, the PDI inhibitor quercetin-3-rutinoside decreased both platelet aggregation and endothelial cell-mediated fibrin generation compared with vehicle. In mice with laser-induced vessel injury, quercetin-3-rutinoside lowered thrombus formation compared with vehicle control, whereas recombinant PDI reversed the inhibitor's antithrombotic effects. Next steps could include testing the inhibitor in additional models of thrombosis.	Patent and licensing status unavailable	Jasuja, R. <i>et al. J. Clin. Invest.</i> ; published online May 8, 2012; doi:10.1172/JCI61228 Contact: Robert Flaumenhaft, Beth Israel Deaconess Medical Center, Boston, Mass. e-mail: rflaumen@bidmc.harvard.edu
Endocrine/metabolic disease				
Diabetes; obesity	Aldehyde dehydrogenase 1 family member A1 (ALDH1A1)	Mice and human tissue studies suggest antagonizing ALDH1A1 could help treat obesity and type 2 diabetes. Obese humans and mice fed a high-fat diet showed greater ALDH1A1 expression in visceral white fat than lean controls. In mice fed a high-fat diet, an <i>Aldh1a1</i> antisense oligonucleotide decreased weight gain and visceral fat mass compared with a control antisense oligonucleotide. The antisense oligonucleotide also improved insulin and glucose tolerance. Next steps include elucidating the mechanisms that underlie the observed effects and exploring how to modulate the target.	Patent and licensing status undisclosed	Kiefer, F.W. <i>et al. Nat. Med.</i> ; published online May 6, 2012; doi:10.1038/nm.2757 Contact: Jorge Plutzky, Brigham and Women's Hospital and Harvard Medical School, Boston, Mass. e-mail: jplutzky@rics.bwh.harvard.edu
Musculoskeletal disease				
Musculoskeletal disease	Family with sequence similarity 20 member C (FAM20C)	<i>In vitro</i> studies identified FAM20C as a protein kinase that phosphorylates extracellular proteins and that could be targeted to treat Raine syndrome, a rare congenital disorder characterized by lethal bone dysplasias. A series of <i>in vitro</i> studies showed that FAM20C is a Golgi casein kinase that phosphorylates proteins for cell secretion, including those involved in bone mineralization. In human osteosarcoma cell lines, mutant forms of FAM20C associated with Raine syndrome showed lower ability to phosphorylate osteopontin (OPN; SPP1), a protein that mediates bone remodeling, than the wild-type protein. Next steps could include screening for compounds that improve FAM20C activity.	Patent and licensing status unavailable	Tagliabracci, V.S. <i>et al. Science</i> ; published online May 10, 2012; doi:10.1126/science.1217817 Contact: Jack E. Dixon, University of California, San Diego, La Jolla, Calif. e-mail: jedixon@ucsd.edu

This week in therapeutics (continued)

Indication	Target/marker/ pathway	Summary	Licensing status	Publication and contact information
Neurology				
Alzheimer's disease (AD)	β -Amyloid 42 (A β 42)	<i>In vitro</i> and mouse studies suggest inhibiting a pyroglutamylated form of A β 42 could help treat AD. In neurons cultured with different A β forms, a mixture of A β 42 plus pyroglutamylated A β 42 caused formation of stable oligomers that were more cytotoxic than either A β form alone. In human AD brain samples, pyroglutamylated A β 42 was found in all three brains, whereas it was found in only one of three age-matched controls. In a mouse model of AD, peri-hippocampal injection of low concentrations of pyroglutamylated A β 42 led to greater plaque accumulation and severity of neurological symptoms than control sham injection. Next steps could include identifying a way to target pyroglutamylated A β 42. SciBX 5(21); doi:10.1038/scibx.2012.554 Published online May 24, 2012	Findings unpatented by the University of Virginia; unavailable for licensing	Nussbaum, J.M. <i>et al. Nature</i> ; published online May 2, 2012; doi:10.1038/nature11060 Contact: George S. Bloom, University of Virginia, Charlottesville, Va. e-mail: gsb4g@virginia.edu
Alzheimer's disease (AD)	Not applicable	A clinical study suggests epilepsy drugs could be useful for treating or preventing AD. In imaging studies, patients with amnesic mild cognitive impairment, a precursor to AD, had higher hippocampal activity than healthy controls. Patients treated with the generic epilepsy drug levetiracetam had lower hippocampal activity and better cognitive performance than their baseline levels. Next steps include optimization of dosing and endpoints for a Phase IIb trial to prevent AD (<i>see Cooling down AD, page 4</i>). SciBX 5(21); doi:10.1038/scibx.2012.555 Published online May 24, 2012	Patented; licensed to AgeneBio Inc.	Bakker, A. <i>et al. Neuron</i> ; published online May 10, 2012; doi:10.1016/j.neuron.2012.03.023 Contact: Michela Gallagher, The Johns Hopkins University, Baltimore, Md. e-mail: michela@jhu.edu
Autism	Metabotropic glutamate receptor subtype 5 (mGluR5; GRM5)	Studies in mice suggest antagonizing mGluR5 could help treat autism. In a mouse model of autism, the negative allosteric mGluR5 modulator GRN-529 (PF-05212391) decreased self-grooming and stereotyped jumping and increased social functioning compared with no treatment. Next steps could include further preclinical evaluation in preparation for clinical trials in autism or fragile X syndrome. Seaside Therapeutics Inc. and Merck & Co. Inc. have the mGluR5 antagonist STX107 in Phase II testing for autism and fragile X syndrome. Other mGluR5 antagonists in Phase II trials for the indication include Novartis AG's AFQ056 and RG7090 from Roche and Chugai Pharmaceutical Co. Ltd. SciBX 5(21); doi:10.1038/scibx.2012.556 Published online May 24, 2012	GRN-529 patented by Pfizer Inc.; licensing status undisclosed	Silverman, J.L. <i>et al. Sci. Transl. Med.</i> ; published online April 25, 2012; doi:10.1126/scitranslmed.3003501 Contact: Jacqueline N. Crawley, National Institute of Mental Health, Bethesda, Md. e-mail: crawleyj@mail.nih.gov Contact: Jill L. Silverman, same affiliation as above e-mail: silvermanj@mail.nih.gov Contact: Robert H. Ring, Autism Speaks, Princeton, N.J. e-mail: robert.ring@autismspeaks.org Contact: Daniel G. Smith, Pfizer Worldwide Research and Development, Groton, Conn. e-mail: daniel.g.smith@pfizer.com

This week in therapeutics (continued)

Indication	Target/marker/pathway	Summary	Licensing status	Publication and contact information
Diabetic neuropathy	Methylglyoxal; NaV1.8 (PN3; SCN10A)	Human and mouse studies suggest inhibiting the metabolite methylglyoxal could help treat hyperalgesia in diabetic neuropathy. Type 2 diabetes patients with pain had greater plasma levels of methylglyoxal than type 2 diabetes patients with no pain or healthy controls. In diabetic and methylglyoxal-treated healthy mice, the metabolite modified Scn10a in nociceptive neurons to increase excitability, which in turn increased thermal and mechanical hypersensitivity compared with what was seen in untreated healthy controls and <i>Scn10a</i> knockdown mice. In the diabetic and methylglyoxal-treated healthy mice, a methylglyoxal-scavenging peptide decreased thermal and mechanical hypersensitivity compared with an inactive control peptide. Ongoing work includes testing the methylglyoxal-scavenging peptide in additional animal models of diabetes. SciBX 5(21); doi:10.1038/scibx.2012.557 Published online May 24, 2012	Patented; unlicensed	Bierhaus, A. <i>et al. Nat. Med.</i> ; published online May 13, 2012; doi:10.1038/nm.2750 Contact: Peter P. Nawroth, Heidelberg University Hospital, Heidelberg, Germany e-mail: peter.nawroth@med.uni-heidelberg.de
Parkinson's disease (PD)	UbiA prenyltransferase domain containing 1 (UBIAD1)	<i>Drosophila</i> studies suggest improving vitamin K ₂ production could help treat diseases involving mitochondrial dysfunction, including PD. Heix, the <i>Drosophila</i> analog of human UBIAD1, converts vitamin K ₁ to vitamin K ₂ in mitochondria. In <i>Drosophila</i> with PD-related mutations, <i>Heix</i> knockouts had greater mitochondrial dysfunction and flight defects than <i>Heix</i> -expressing controls. In the <i>Heix</i> knockout <i>Drosophila</i> with PD-related mutations, <i>Heix</i> overexpression or vitamin K ₂ supplementation restored mitochondrial function. Next steps include determining the role of vitamin K ₂ in other small animal models of PD. SciBX 5(21); doi:10.1038/scibx.2012.558 Published online May 24, 2012	Findings unpatented; available for licensing	Vos, M. <i>et al. Science</i> ; published online May 10, 2012; doi:10.1126/science.1218632 Contact: Patrik Verstreken, Catholic University Leuven, Leuven, Belgium e-mail: patrik.verstreken@med.kuleuven.be
Stroke	Transglutaminase 1 (TGM1; TG1); TGM2 (TG2)	Studies in mice and in cultured neurons suggest inhibiting TGM1 and TGM2 could be neuroprotective after stroke. In mouse models of brain ischemia and oxidatively stressed cortical neurons, <i>Tgm1</i> and <i>Tgm2</i> expression was induced. In the cultured rat neurons, a nonspecific transglutaminase peptide inhibitor or cystamine decreased levels of <i>Tgm1</i> and <i>Tgm2</i> expression and neuronal death compared with no treatment. Ongoing work includes developing a neuron-specific conditional knockout for <i>Tgm1</i> in mice to be tested in stroke and HD models. Raptor Pharmaceutical Corp.'s RP103 (DR Cystamine) is in Phase II testing to treat Huntington's disease (HD). SciBX 5(21); doi:10.1038/scibx.2012.559 Published online May 24, 2012	Unpatented; licensing status not applicable	Basso, M. <i>et al. J. Neurosci.</i> ; published online May 9, 2012; doi:10.1523/JNEUROSCI.3353-11.2012 Contact: Rajiv R. Ratan, Burke Rehabilitation Hospital, White Plains, N.Y. e-mail: rratan@burke.org Contact: Manuela Basso, same affiliation as above e-mail: mbasso@burke.org

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			
High throughput screening of T cell receptor (TCR) to detect minimal residual disease (MRD) in T cell acute lymphoblastic leukemia (T-ALL)	High throughput screening of lymphoid receptor genes could help guide diagnosis and prognosis in T-ALL. In samples from 43 patients with T-ALL taken before chemotherapy, sequencing the T cell receptor β -chain (TCRB) detected clonal rearrangements in 31 samples. In this subset of patients, sequencing of TCRB in samples taken after chemotherapy detected clonal rearrangements in 22 of 31 cases, suggesting MRD. Conventional flow cytometry only detected MRD in 10 of the 31 cases. In the samples, TCRB rearrangements correlated with less aggressive T-ALL phenotypes. Next steps include expanding the patient population, following the patients for a longer period of time and correlating MRD detection with survival.	Patent applications filed covering the screening technology, called immunoSEQ; exclusively licensed to Adaptive Biotechnologies Corp.	Wu, D. <i>et al. Sci. Transl. Med.</i> ; published online May 16, 2012; doi:10.1126/scitranslmed.3003656 Contact: Harlan Robins, Fred Hutchinson Cancer Research Center, Seattle, Wash. e-mail: hrobins@fhcrc.org Contact: Brent L. Wood, University of Washington, Seattle, Wash. e-mail: woodbl@u.washington.edu
	SciBX 5(21); doi:10.1038/scibx.2012.560 Published online May 24, 2012		
Proteomic method for developing rational combinations of kinase inhibitors	A proteomic method could aid the development of rational combinations of kinase inhibitors to treat cancer. A mass spectrometry method profiled the activities of kinases in cell lines and in a genetically engineered mouse model of triple-negative breast cancer before and after treatment with AZD6244. The approach identified AZD6244-induced increases in the activity of multiple kinases, including those known to be blocked by Nexavar sorafenib. In the mouse model, AZD6244 plus Nexavar increased tumor regression compared with either agent alone. Next steps include using the approach to look at changes in kinase activities in the tumor tissue of patients with breast cancer treated with trametinib. AstraZeneca plc and Array BioPharma Inc. are running Phase II studies of the MAP kinase kinase 1 (MAP2K1; MEK1) and MAP2K2 (MEK2) dual inhibitor AZD6244 (ARRY-886) for multiple cancers. At least nine other companies have MEK1 and/or MEK2 inhibitors in clinical testing in cancer. Nexavar sorafenib, a multitargeted kinase inhibitor from Onyx Pharmaceuticals Inc. and Bayer AG, is marketed to treat advanced renal cell carcinoma (RCC) and hepatocellular carcinoma.	Patent application filed covering technology; available for licensing	Duncan, J.S. <i>et al. Cell</i> ; published online April 13, 2012; doi:10.1016/j.cell.2012.02.053 Contact: Gary L. Johnson, The University of North Carolina at Chapel Hill School of Medicine, Chapel Hill, N.C. e-mail: glij@med.unc.edu
	SciBX 5(21); doi:10.1038/scibx.2012.561 Published online May 24, 2012		
Chemistry			
Synthesis of biologically active meroterpenoids	A method of synthesizing meroterpenoids could generate new compounds to treat cancer and infectious diseases. A five-step reaction sequence produced gram-scale quantities of a meroterpenoid precursor, and a six-step sequence produced gram-scale quantities of a meroterpenoid intermediate. Additional reaction sequences converted the precursor or the intermediate into 9 known meroterpenoids in overall yields of 8%–33%, including those with antimicrobial and anticancer properties. Ongoing collaborations with Leo Pharma A/S include using the method to synthesize and test the biological activity of other meroterpenoids.	Unpatented; unlicensed	Dixon, D.D. <i>et al. J. Am. Chem. Soc.</i> ; published online May 14, 2012; doi:10.1021/ja303937y Contact: Phil S. Baran, The Scripps Research Institute, La Jolla, Calif. e-mail: pbaran@scripps.edu
	SciBX 5(21); doi:10.1038/scibx.2012.562 Published online May 24, 2012		

This week in techniques (continued)

Approach	Summary	Licensing status	Publication and contact information
Drug platforms			
Protocol for augmenting β cell regeneration and reversing late-stage type 1 diabetes	A protocol using an antibody and a cell transplant conditioning regimen plus delivery of gastrin and epidermal growth factor (EGF) could help treat late-stage type 1 diabetes. The protocol involves delivering anti-CD3 and anti-CD8A (p32; CD8) antibodies followed by transplantation with donor bone marrow and CD4 ⁺ -depleted spleen cells, followed by daily injections of gastrin and EGF for up to 60 days. In a mouse model of late-stage type 1 diabetes, the protocol restored normal glycemia in 7 of 12 animals for up to 150 days, whereas conditioning regimen or gastrin plus EGF alone did not restore normal glycemia in any animals. Next steps include optimizing the growth factor regimen and evaluating the combination approach in large animal models.	Conditioning regimen covered by issued and pending patents; available for licensing from City of Hope Contact: Matthew Grunseth, City of Hope, Duarte, Calif. e-mail: mgrunseth@coh.org	Wang, M. <i>et al. Sci. Transl. Med.</i> ; published online May 9, 2012; doi:10.1126/scitranslmed.3003835 Contact: Defu Zeng, Beckman Research Institute at City of Hope, Duarte, Calif. e-mail: dzeng@coh.org
	SciBX 5(21); doi:10.1038/scibx.2012.563 Published online May 24, 2012		

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

Company and institution index**A**

Abbott Laboratories 1
 ActivX Biosciences Inc. 7
 Adaptive Biotechnologies Corp. 16
 AgeneBio Inc. 4,14
 Amgen Inc. 7
 Array BioPharma Inc. 16
 Astellas Pharma Inc. 12
 Astex Pharmaceuticals Inc. 2
 AstraZeneca plc 16

B

Bayer AG 16
 Beatson Institute for Cancer Research 2
 Beth Israel Deaconess Medical Center 6
 Bristol-Myers Squibb Co. 7

C

Cellzome AG 6
 Chugai Pharmaceutical Co. Ltd. 10,14
 City of Hope 17

D

Daiichi Sankyo Co. Ltd. 10

E

Edison Pharmaceuticals Inc. 12
 EntreChem S.L. 10
 Evotec AG 7
 Exelixis Inc. 6

G

Genentech Inc. 1
 Gilead Sciences Inc. 7
 Gladstone Institute of Neurological Disease 4
 GlaxoSmithKline plc 6

H

Hanmi Pharmaceutical Co. Ltd. 11
 Hannover Medical School 6
 Harvard Medical School 5
 Howard Hughes Medical Institute 6

I

Infinity Pharmaceuticals Inc. 7

J

Johns Hopkins University 4
 Johnson & Johnson 12

K

Karus Therapeutics Ltd. 7

L

Leo Pharma A/S 16

M

Massachusetts General Hospital 6
 Merck & Co. Inc. 7,14
 Mundipharma International Ltd. 7

N

Novartis AG 7,14

O

Onyx Pharmaceuticals Inc. 10,16

P

Pathway Therapeutics Inc. 7
 Pfizer Inc. 6,10,11,14

R

Raptor Pharmaceutical Corp. 15
 Roche 1,8,10,14

S

Sanofi 8
 Seaside Therapeutics Inc. 14
 State University of New York at Stony Brook 8
 StemPAR Sciences Inc. 12

T

Takeda Pharmaceutical Co. Ltd. 7,12

U

UCB Group 4
 University of California, San Francisco 4
 University of Fribourg 8
 University of Pittsburgh 12
 University of Virginia 14

V

Vanderbilt University School of Medicine 1
 Vernalis plc 2

W

Washington University in St. Louis 4

Y

Yakult Honsha Co. Ltd. 11

.....

Target and compound index**A**

A β 4,14
 A β 42 14
 ABCB1 11
 ABT-263 1
 ACE 5
 ACK1 12
 AFQ056 14
 Aldehyde dehydrogenase 1 family member A1 13
 ALDH1A1 13
 AMG 319 7
 Angiotensin-converting enzyme 5
 ARF 10
 ARRY-886 16
 ATP 7
 Axitinib 6
 AZD6244 16

B

β -Amyloid 4
 β -Amyloid 42 14
 β -Lapachone 12
 B cell lymphoma 2 1
 BCL-2 1
 BCL2 1
 BEZ235 8
 BIRC5 12
 Bis(indenoisoquinoline) 11

Bortezomib 12
 BRAF 10
 BYL719 8

C

Cabozantinib 9
 Camptosar 11
 Camptothecin 11
 CD3 17
 CD4 17
 CD8 17
 CD8A 17
 CD243 11
 CDK4 10
 CDK6 10
 CDKN2A 10
 Cisplatin 10
 c-Met receptor tyrosine kinase 9
 Cyclin dependent kinase 4 10
 Cyclin dependent kinase inhibitor 2A 10
 CZC19091 8
 CZC24832 8

D

Dasatinib 7
 Deoxyriboquinone 12
 DNA-dependent protein kinase 8
 DNA-PK 8
 DNQ 12
 DR Cystamine 15

E

Ecdysteroid 11
 EGF 2,17
 EGFR 3
 EGF receptor 3
 EPI-743 12
 Epidermal growth factor 2,17

F

FAM20C 13
 Family with sequence similarity 20 member C 13
 FLT1 5
 FRAP 8
 FTDP-17 4

G

GABA_A receptor 5
 GDC-0941 8
 GEF 1
 Gleevec 7
 GRM5 14
 GRN-529 14
 GS-1101 7
 GTP binding protein 1
 Guanine nucleotide exchange factor 1

H

H3K18 11
 Heix 15
 HGFR 9
 HRAS 1

I

IL-17 8
 Imatinib 7
 INK4a 10
 INK1117 7

Inlyta 6
 IPI-145 7
 Irinotecan 11

K

KAR4139 7
 KAR4141 7
 Keppra 4
 KiNativ 7
 Kinaxo 7
 Kinobeats 7
 K-Ras 1,10

L

Levetiracetam 4,14

M

Mammalian target of rapamycin 8
 MAP2K1 16
 MAP2K2 16
 MAP kinase kinase 1 16
 MAPT 4
 MDR1 11
 MEK1 16
 MEK2 16
 Meroterpenoid 16
 MET 9
 Metabotropic glutamate receptor subtype 5 14
 Methylglyoxal 15
 mGluR5 14
 Microtubule-associated protein- τ 4
 Mithramycin 10
 mTOR 8

N

NAD(P)H dehydrogenase 12
 quinine 1 12
 NaV1.8 15
 Navitoclax 1
Neuroblastoma Ras viral (v-Ras) oncogene 1
 Nexavar 16
 NQO1 12
 NRAS 1

O

OPN 13
 Oratecan 11
 Oraxol 11
 Osteopontin 13

P

p16INK4a 10
 p21 Protein (Cdc42 Rac)-activated kinase 4 11
 p32 17
 Paclitaxel 11
 PAK4 11
 Pazopanib 6
 PD-0332991 10
 PDI 13
 Peroxisome proliferation-activated receptor- γ coactivator 1 α 5
 PF-05212391 14
 PGC-1 α 5
 P glycoprotein 11
 P-gp 11
 Phosphatidylinositol-3,4,5-triphosphate-dependent Rac exchange factor 2 12

Phosphoinositide 3-kinase	6	Ras	1	T			
Phosphoinositide 3-kinase- α	8	RG7090	14	TAU	4	UbiA prenyltransferase domain containing 1	15
Phosphoinositide 3-kinase- δ	7	Rituxan	1	T cell receptor	16		
PI3K	6	Rituximab	1	T cell receptor β -chain	16	V	
PI3K α	6	ROR γ 2	8	TCR	16	VEGF	9
PI3K β	6	ROR γ T	8	TCRB	16	VEGFR-1	5
PI3K δ	6	RP103	15	TDP1	11	VEGF receptor 1	5
PI3K γ	6			TG1	15	Velcade	12
PN3	15			TG2	15	Vemurafenib	10
PPARGC1A	5	S		TGM1	15	<i>v-Ha-ras Harvey rat sarcoma viral oncogene homolog</i>	1
PREX2	12	SCN10A	15	TGM2	15	Votrient	6
Protein disulfide isomerase	13	sFLT1	5	Th17	8		
PWT33597	8	SIRT7	11	T helper type 17	8		
Pyroloaminopyrazole	11	Sirtuin 7	11	Tnk2	12	X	
		Soluble FLT1	5	TOP1	11	XL184	9
		Son of sevenless homolog 1	1,10	Topoisomerase I	11	XL499	7
		Sorafenib	16	Trametinib	16	XL765	8
Q		SOS1	1,10	Transglutaminase 1	15		
QR1	12	SPP1	13	Tyrosine kinase non-receptor 2	12	Y	
Quercetin-3-rutinoside	13	Sprycel	7	Tyrosyl-DNA phosphodiesterase 1	11	YM155	12
		STX107	14	U		Z	
R		Survivin	12	UBIAD1	15	Zelboraf	10
RAFT1	8	SV2A	4				
RAR-related orphan receptor C thymus-specific isoform	8	Synaptic vesicle protein	4				