

THIS WEEK

ANALYSIS

COVER STORY

1 **Cancer target selection pressure**

An Institute of Cancer Research team has developed a computational algorithm that hones in on cancer targets with the desired mix of biological validation and druggability. The approach could help prioritize targets.

TARGETS & MECHANISMS

4 **Statins for fragile X**

MIT researchers have shown that the widely used cholesterol drug lovastatin can correct fragile X syndrome in mice. The findings add to a growing list of unconventional strategies for this common form of mental retardation.

5 **Stressing out over depression and anxiety**

Two teams have shown that enhanced glucocorticoid signaling in the brain triggers aberrant behavior in mouse models of depression and anxiety. The groups are now studying the mechanisms underlying the effect to determine whether blocking glucocorticoid signaling could treat neuropsychiatric diseases.

TOOLS

7 **Tethered capsule endomicroscopy**

Massachusetts General Hospital researchers have created a tethered, capsule-size endoscope that can generate 3D microstructural images of the upper GI tract. The team used the device to image Barrett's esophagus in patients and has licensed the technology to NinePoint Medical.

THE DISTILLERY

9 **This week in therapeutics**

Treating angiotensin II-overexpressing NSCLCs with ACE inhibitors; regenerating β cell mass in type 1 diabetes with diarylurea-based compounds; reducing fevers with ADRA2 agonists; and more...

13 **This week in techniques**

High-throughput shRNA-based genetic interaction mapping in human cells; patient iPS cell-derived cardiomyocytes as models for right ventricular dysplasia/cardiomyopathy; highly prevalent *TERT* promoter mutations in melanoma; and more...

INDEXES

16 **Company and institution index**

16 **Target and compound index**

Cancer target selection pressure

By *Joanne Kotz, Senior Editor*

Cancer drug discovery does not suffer from a dearth of targets—instead it is in need of a way to prioritize target selection. Now, a team from **The Institute of Cancer Research** has created a computational algorithm that hones in on targets with strong biological validation that also are predicted to be druggable.¹ The approach may provide a basis for systematically picking cancer targets.

Currently, decisions about cancer target selection are usually based on “gut feeling,” said Stephen Friend, president, cofounder and director at **Sage Bionetworks** and former SVP and franchise head for oncology research at **Merck & Co. Inc.** “The calculus of how people weigh certain aspects of the decision—am I looking for strong valid biology, or does druggability trump all—is almost done as if we were alchemists.”

A team led by Paul Workman and Bissan Al-Lazikani wanted to develop a platform to objectively compare the strengths and weaknesses associated with potential cancer targets.

Workman is deputy chief executive of The Institute of Cancer Research (ICR), head of ICR's division of cancer therapeutics and director of ICR's **Cancer Research UK** Cancer Therapeutics Unit. Al-Lazikani leads the computational biology and chemogenomics team in both the unit and the Division of Cancer Therapeutics at ICR.

“The massive and continual daily dump of cancer data far exceeds our ability to do detailed wet biology follow-up. The status quo is that the selection of targets to work on starts from an initial choice that is highly biased, such as which pathways or targets are familiar” to a given researcher, said Workman. “We felt there was a real need to be more unbiased and systematic and to do assessments rapidly and at scale at the most critical stage of drug discovery—choosing what targets to work on at the beginning.”

“This is very important as each target can take a year or more to validate—or not—and the failure rate is high,” Workman added.

As proof of principle, the computational approach developed by the ICR team focused on targets previously implicated in cancer and integrates multiple types of information to estimate the likelihood that a target will be druggable. The information includes target class, small molecule bioactivity data for the target that has been curated from published literature and analysis of potential small molecule binding sites based on experimentally determined protein structures or homology models.

From a list of 479 genes known to be altered in cancer, the method identified 29 oncogenes and 16 tumor suppressors that were predicted

**EDITORIAL****Editor-in-Chief:** Karen Bernstein, Ph.D.**Managing Editor:** Gaspar Taronger-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 Taronger-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 Inchoombe, Managing Director, Nature Publishing Group; Peter Collins, Ph.D., Publishing Director, NPG; Christoph Hesselmann, Ph.D., Chief Financial Officer, NPG.

Copyright © 2013 Nature Publishing Group ALL RIGHTS RESERVED.

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

to be druggable but for which few or no small molecule ligands have yet been reported. This result suggests that these targets are relatively unexplored but potentially tractable for small molecule drug discovery.

The method was published in *Nature Reviews Drug Discovery*.

“The factors considered in this approach are ones that have been debated at the initiation of projects in pharma for many years. Unfortunately, these debates are often ad hoc in terms of the context in which an individual target is assessed. The contribution of this methodology is in providing a systematic and unbiased method for target assessment that can be scaled to any number of targets,” said Stephen Frye, director of the Center for Integrative Chemical Biology and Drug Discovery at **The University of North Carolina at Chapel Hill Eshelman School of Pharmacy**.

“By combining biological validity and chemical tractability, this approach balances the debate in a helpful way and directs it toward practical drug discovery. At the very least, the risks in a portfolio of targets can be identified and targets ranked against them. In the end you make a decision based on a much more complex set of data than this, but as a first cut this provides an unbiased, comprehensive look,”

“By combining biological validity and chemical tractability, this approach balances the debate in a helpful way and directs it toward practical drug discovery. At the very least, the risks in a portfolio of targets can be identified and targets ranked against them.”

— Stephen Frye,

*The University of North Carolina
at Chapel Hill Eshelman
School of Pharmacy*

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

added Frye, who was previously worldwide VP of discovery medicinal chemistry at **GlaxoSmithKline plc**.

“If you were to give this to the heads of oncology at multiple pharmas, they would argue with the components or the weighing, but that wouldn’t make this more right or more wrong. What this paper says is: here is a roadmap, a series of decisions that need to all be weighed,” Friend told *SciBX*.

Expanding the dialog

A key next step for expanding the utility of the algorithm will be incorporating additional clinical data, said Workman. The next version, which will be released this summer, will include all of the genomic and expression data from the International Cancer Genome Consortium. This additional clinical data will expand the algorithm to help compare the level of biological validation of potential targets in addition to weighing likely druggability.

Friend noted that “there is a fair amount of data already included in the algorithm, but it’s 1% of what could be in there.”

Workman’s team also plans to further refine the algorithm’s ability to predict druggability.

Indeed, Frye said, “the druggability score is a fairly crude estimate for what is possible.” For instance, he said, histone acetyltransferases come up as potentially druggable, but “people have been working on them for years and there still are not good inhibitors.”

The algorithm also may miss druggable targets. The methyllysine-binding protein L(3)mbt-like 3 (L3MBTL3) was predicted to not be druggable. However, Frye and colleagues recently reported the first inhibitor of the target.² Their molecule binds to a pocket that is only accessible when the target dimerizes and thus is not easily predicted by current algorithms.

“This is not target selection by computer,” noted Workman. “The idea is to have all the data in front of you. You can look for those targets that

are biologically really appealing, and then depending on your appetite for risk you can go for targets where there is chemical matter available or ones that are predicted to be druggable to varying degrees but have no chemical matter.”

Workman said ICR is using the algorithm to prioritize its basket of identified potential drug targets, including those found via cancer genomics efforts and synthetic lethal screens in cancer cell lines.

The team looks for targets ranked toward the top by the algorithm and then chooses 5 or 10 targets to explore with more intensive wet biology experiments before making a final decision about which targets to pursue.

The method reported in the paper is unpatented and is freely available through the ICR’s [canSAR](#) database.

Kotz, J. *SciBX* 6(6); doi:10.1038/scibx.2013.128

Published online Feb. 14, 2013

REFERENCES

- Patel, M.N. *et al. Nat. Rev. Drug Discov.*; published online Dec. 31, 2012; doi:10.1038/nrd3913
Contact: Bissan Al-Lazikani, The Institute of Cancer Research, London, U.K.
 e-mail: bissan.al-lazikani@icr.ac.uk
Contact: Paul Workman, same affiliation as above
 e-mail: paul.workman@icr.ac.uk
- James, L.I. *et al. Nat. Chem. Biol.*; published online Jan. 6, 2013; doi:10.1038/nchembio.1157

COMPANIES AND INSTITUTIONS MENTIONED

Cancer Research UK, London, U.K.

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

The Institute of Cancer Research, Sutton, U.K.

Merck & Co. Inc. (NYSE:MRK), Whitehouse Station, N.J.

Sage Bionetworks, Seattle, Wash.

The University of North Carolina at Chapel Hill Eshelman School of Pharmacy, Chapel Hill, N.C.

SciBX: Science–Business eXchange

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

Can you afford not to subscribe?

Visit scibx.com for details on how to subscribe to SciBX

Statins for fragile X

By Lev Osherovich, Senior Writer

Researchers at the **Massachusetts Institute of Technology** have mouse data showing that the cholesterol drug lovastatin can correct fragile X syndrome.¹ The findings add to a growing list of unconventional strategies for treating this common form of mental retardation.

Fragile X syndrome is caused by trinucleotide repeat expansions in *fragile X mental retardation 1 (FMR1)*. The condition causes alterations in protein synthesis in neurons, leading to developmental delays, autism and epilepsy.

FMR1's normal function is to negatively regulate protein synthesis. Indeed, *Fmr1* knockout mice generally exhibit increased protein levels. Thus, therapeutic strategies for the condition have aimed to lower overall rates of protein synthesis by hitting translation factors and brain receptors that regulate translation.²

Three companies—**Novartis AG** and **Roche** and partner **Seaside Therapeutics Inc.**—have clinical-stage compounds for fragile X syndrome that target such brain receptors.

Now, a team led by Mark Bear, professor of neuroscience at MIT and an investigator at the **Howard Hughes Medical Institute**, has shown that lovastatin can lower protein synthesis in the brain and correct at least one mouse-specific manifestation of fragile X syndrome—epileptic seizures caused by loud noises.

Brain chilling

Bear's team strung together prior evidence to formulate the hypothesis that statins could help treat fragile X.

In the 1990s, several teams showed that statins reduced farnesylation of Ras and the activity of two downstream kinases, MAP kinase 3 (MAPK3; ERK-1) and MAPK1 (ERK-2), in cells.³ In 2010, Bear's team showed that blocking Ras-ERK-1/ERK-2 signaling decreased overall protein synthesis in a mouse model of fragile X.⁴

“What made us pursue lovastatin was that this is a widely used drug in clinical practice with a well-known safety profile that is even used in children,” said Bear.

His team found that brain tissue from *Fmr1* knockout mice treated with lovastatin had lower levels of active ERK-1 and ERK-2 and less protein synthesis than tissue from vehicle-treated controls. In cultured brain slices, lovastatin corrected the defective responsiveness to electrical stimulus found in *Fmr1* knockouts.

The team then tested the effects of lovastatin on electrophysiological excitability of brain tissue from *Fmr1* knockouts. Brain slices from the visual cortex of *Fmr1* knockout mice treated with lovastatin had a higher threshold of excitation than slices from vehicle-treated controls. Altogether, lovastatin made the brain slices of *Fmr1* knockouts behave similarly to those from wild-type mice.

Lovastatin's moderating effect on brain activity led to lower susceptibility to noise-induced seizures than vehicle.

“Lovastatin could correct the excess protein synthesis in our mouse

model of fragile X and could correct the audiogenic seizure phenotype that's a robust feature of this model,” said Bear.

The findings were reported in *Neuron*.

Statin' the case

The findings suggest statins could fit into a treatment regimen for fragile X syndrome, but it is unclear whether the compounds could work as monotherapy or as adjuncts to other translation-lowering treatments.

Statins inhibit HMG-CoA reductase, a biosynthetic enzyme that is several steps upstream of ERK-1 and ERK-2. Thus, the molecules are fairly indirect inhibitors of ERK-1 and ERK-2 activity. In contrast, brain receptor antagonists are thought to hit fragile X-related translational mechanisms more directly.

Seaside cofounder, president and CEO Randall Carpenter suggested statins could prove useful in a subset of patients with fragile X syndrome that have severe seizures. “This paper was largely focused on epileptogenesis and excitability in seizure models,” noted Carpenter. “About 20%–30% of people with fragile X mutations also have a seizure disorder.”

Seaside and Roche are developing the biotech's arbaclofen (STX-209), a GABA_B receptor antagonist that is in two Phase III trials for fragile X syndrome and has completed a Phase II trial for autism spectrum disorder (ASD). Seaside will report the ASD data this year.

Seaside was cofounded by Bear and has not licensed his statin discoveries.

Carpenter said it is not clear why some patients with fragile X have epilepsy and others do not, but Bear's findings suggest statins could be an add-on therapy for patients in the former camp.

Seaside and Roche also are co-developing RG7090, an antagonist of metabotropic glutamate receptor subtype 5 (mGluR5; GRM5) that is in Phase II trials for fragile X syndrome. Seaside's STX-107, another mGluR5 antagonist, is in Phase II testing for fragile X.

Novartis' AFQ056, another mGluR5 antagonist, is in Phase III trials for fragile X.

Carpenter said GABA_B and mGluR5 are well-validated targets that reduce the translation of a broad range of proteins and that it remains to be seen whether inhibiting Ras-ERK-1/ERK-2 signaling with statins would have a comparably protective effect.

Indeed, because lovastatin had a big effect on audiogenic seizure but only a modest effect on Ras-ERK-1/ERK-2 signaling, the compound could be working through other mechanisms.

“It's possible that lovastatin could be doing more than just inhibiting ERK-1 and ERK-2—it depletes farnesylation in the brain, so there may be other targets,” said Bear.

He now plans to test lovastatin in other murine and tissue culture assays of fragile X syndrome to see whether the compound affects the cognitive aspects of the disease. He also plans to compare the efficacy of statins with that of mGluR5 antagonists.

Carpenter said that instead of statins, it might be more effective to develop compounds that directly hit translational regulatory kinases like ERK-1 and ERK-2.

Indeed, one such kinase—p21 protein (Cdc42 Rac)-activated kinase 1

(Continues on p. 5)

“What made us pursue lovastatin was that this is a widely used drug in clinical practice with a well-known safety profile that is even used in children.”

—Mark Bear,
Massachusetts Institute of
Technology

Stressing out over depression and anxiety

By **Tim Fulmer**, Senior Writer

Two teams have shown that enhanced glucocorticoid signaling in the brain triggers aberrant behavior in mouse models of depression and anxiety.^{1,2} The groups are now using the mice to study the mechanisms underlying the effect and determine whether blocking glucocorticoid signaling can treat neuropsychiatric diseases.

All mammals respond to stress by releasing glucocorticoids from the adrenal glands. Although that stress mechanism is beneficial when it facilitates the fight or flight response, chronic activation of the glucocorticoid response can trigger multiple neuropsychiatric disorders in humans, including pathological anxiety, depression and addiction.

The challenge has been identifying the molecular mechanisms underlying chronic activation of the glucocorticoid-mediated stress response and determining whether blocking that mechanism could help treat those disorders. Moreover, because the glucocorticoid receptor (GCCR) is a transcription factor expressed in many different cell types, safely targeting it in neuropsychiatric disorders will require selectively hitting specific neurons in the brain.

To tackle those issues, two groups generated genetically altered mice and subjected them to environmental conditions predicted to trigger stress-mediated anxiety and depression in humans.

The French group, led by François Tronche and Jacques Barik, built on their prior work that showed selectively knocking out *Gccr* in

postsynaptic, dopamine-sensing neurons decreased cocaine addiction in mice compared with what was seen in control mice.³ Dopamine signaling in the mesolimbic pathway mediates the addictive properties of cocaine and other drugs of abuse.

Tronche is director of research at the **Pierre and Marie Curie University**. Barik is a researcher at the university.

In the new work, Tronche and colleagues used the same mice to study whether selective *Gccr* knockout had a broader protective effect on mice undergoing chronic stress.

Indeed, in animals subjected to repeated social defeat, selective knockout of *Gccr* in postsynaptic, dopamine-sensing neurons led to normal social interactions, whereas wild-type animals showed significantly increased anxiety and social aversion ($p < 0.01$).

Moreover, the effects were localized to the postsynaptic neurons, as selective knockout of *Gccr* in presynaptic, dopamine-releasing neurons failed to protect the same animals from anxiety and social avoidance.

Subsequent mechanistic studies showed that protective *Gccr* knockout in postsynaptic neurons also decreased neurotransmission between pre- and postsynaptic dopamine neurons. That suggested pharmacological blockade of dopamine neuron activity might improve social interactions of wild-type mice following social defeat.

In wild-type mice undergoing repeated social defeat, injection of quinpirole, a generic small molecule that suppresses dopamine neuron activity, increased social interactions compared with injection of saline ($p < 0.001$).

In the second paper, a Japanese and American group hypothesized that environmental stresses in adolescence could be risk factors for depression and anxiety in adulthood.

To test that idea, a team led by Toshitaka Nabeshima and Akira Sawa generated transgenic mice expressing *disrupted in schizophrenia 1*

(Continues on p. 6)

(Continued from "Statins for fragile X," p. 4)

(PAK1)—is the target of preclinical compounds from **Afraxis Inc.** for fragile X syndrome.

Carpenter said such strategies raise concerns about safety and selectivity because of the importance of these targets in the normal functioning of other tissues.

Afraxis CEO Jay Lichter said ERK-1 and ERK-2 are likely to be upstream of PAK1 in the kinase cascade that governs translation levels. He added that hitting this pathway indirectly with statins is an attractive option from a safety standpoint.

"I don't think an ethics board would have a problem giving this to kids," said Lichter.

Along those lines, a Canadian team has started a small open-label dose-ranging study of lovastatin in patients with fragile X who are 10–40 years old.

Lichter noted that besides fragile X syndrome, PAK1 is an attractive target in a range of inflammatory and cancer indications. Last month, Afraxis sold its portfolio of PAK1 inhibitors to Roche's **Genentech Inc.** unit. Genentech did not disclose its development plans for Afraxis' fragile X compounds.

There are patents pending on the findings reported in *Neuron*, and the findings are available for licensing.

Osheroich, L. *SciBX* 6(6); doi:10.1038/scibx.2013.129
Published online Feb. 14, 2013

REFERENCES

- Osterweil, E.K. *et al. Neuron*; published online Jan. 23, 2013; doi:10.1016/j.neuron.2012.01.034
Contact: Mark F. Bear, Massachusetts Institute of Technology, Cambridge, Mass.
e-mail: mbear@mit.edu
- Bhakar, A.L. *et al. Annu. Rev. Neurosci.* **35**, 417–443 (2012)
- Liao, J.K. & Laufs, U. *Annu. Rev. Pharmacol. Toxicol.* **45**, 89–118 (2005)
- Osterweil, E.K. *et al. J. Neurosci.* **30**, 15616–15627 (2012)

COMPANIES AND INSTITUTIONS MENTIONED

Afraxis Inc., La Jolla, Calif.
Genentech Inc., South San Francisco, Calif.
Howard Hughes Medical Institute, Chevy Chase, Md.
Massachusetts Institute of Technology, Cambridge, Mass.
Novartis AG (NYSE:NVS; SIX:NOVN), Basel, Switzerland
Roche (SIX:ROG; OTCQX:RHHBY), Basel, Switzerland
Seaside Therapeutics Inc., Cambridge, Mass.

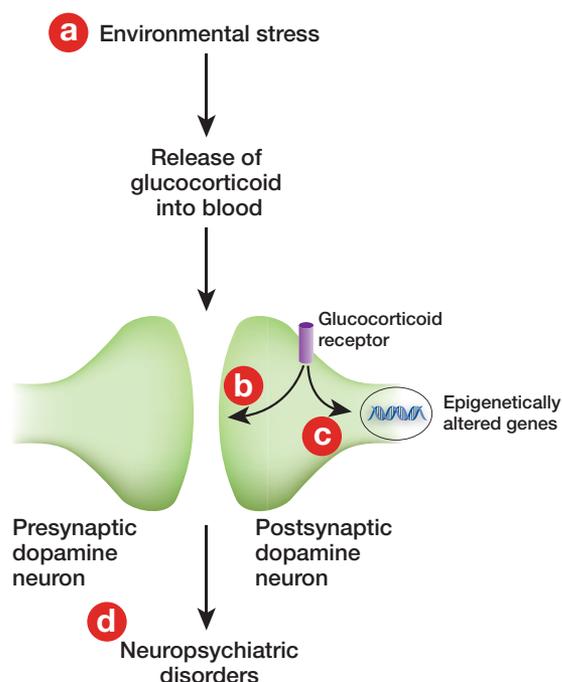


Figure 1. Dopamine stressed out over glucocorticoids.

Environmental triggers induce the release of plasma glucocorticoids [a], which influence dopamine signaling in the brain by either directly altering dopamine neurotransmission between cells [b] or indirectly altering the epigenetic properties of genes involved in dopamine biosynthesis [c]. The resulting alterations lead to behavioral aberrations indicative of anxiety and depression [d].

(*DISC1*), a gene implicated in the development of depression and schizophrenia,⁴ and subjected the adolescent animals to three weeks of isolation stress.

Nabeshima is professor of pharmacy at **Meijo University**. Sawa is professor of psychiatry and director of the Johns Hopkins Schizophrenia Center at **The Johns Hopkins University School of Medicine**.

The resulting animals showed significantly increased social deficits in multiple behavioral tests compared with wild-type controls ($p < 0.01$). The mice also had greater levels of dopamine and tyrosine hydroxylase (TH; TYH) in the frontal cortex. TH catalyzes the rate-limiting step in the synthesis of dopamine.

The increased dopamine levels were associated with greater plasma levels of the glucocorticoid corticosterone.

Based on the findings, the researchers next hypothesized that increased glucocorticoid levels might underlie the higher dopamine levels and thus indirectly drive the behavioral aberrations.

Indeed, in the same mice subjected to isolation stress, a small molecule GCCR antagonist normalized dopamine levels and improved social behaviors, whereas vehicle control had no effect.

Finally, genomic analysis of the mouse models revealed epigenetic alterations associated with isolation stress. Methylation of the promoter region of *TH* was significantly greater than that seen for the same gene in normal control animals ($p < 0.01$). Importantly, the same GCCR antagonist normalized DNA methylation levels of the gene.

In conclusion, the authors of the second paper wrote that their mice “may be a promising model for psychotic depression” and “could provide a good template not only for screening compounds with better efficacy and fewer side effects but also for prophylactic environmental readjustment.”

Taken together, the two papers published back-to-back in *Science* suggest a mechanism whereby environmental triggers induce the release of plasma glucocorticoids, which then influence dopamine signaling in the brain by either directly altering dopamine neurotransmission between cells or indirectly altering the epigenetic properties of genes involved in dopamine biosynthesis. In either case, the resulting alterations lead to behavioral aberrations indicative of anxiety and depression (see Figure 1, “Dopamine stressed out over glucocorticoids”).

The French group now plans to test strategies for selectively antagonizing GCCR in postsynaptic, dopamine-sensing neurons as well as approaches for decreasing the activity of dopamine neurons to reduce social aversion, co-corresponding author Tronche told *SciBX*.

The Japanese group plans to use its mice to determine whether the observed epigenetic alterations are limited to *TH* or also include other genes, said co-corresponding author Sawa.

The findings in both papers are not covered by IP and are unavailable for licensing.

Fulmer, T. *SciBX* 6(6); doi:10.1038/scibx.2013.130

Published online Feb. 14, 2013

REFERENCES

- Barik, J. *et al. Science*; published online Jan. 18, 2013; doi:10.1126/science.1226767
Contact: François Tronche, Pierre and Marie Curie University, Paris, France
e-mail: francois.tronche@upmc.fr
Contact: Jacques Barik, same affiliation as above
e-mail: jacques.barik@snv.jussieu.fr
- Niwa, M. *et al. Science*; published online Jan. 18, 2013; doi:10.1126/science.1226931
Contact: Akira Sawa, The Johns Hopkins University School of Medicine, Baltimore, Md.
e-mail: asawa1@jhmi.edu
Contact: Toshitaka Nabeshima, Meijo University, Nagoya, Japan
e-mail: tnabeshi@meijo-u.ac.jp
- Ambroggi, F. *et al. Nat. Neurosci.* **12**, 247–249 (2009)
- Brandon, N.J. *et al. J. Neurosci.* **29**, 12768–12775 (2009)

COMPANIES AND INSTITUTIONS MENTIONED

The Johns Hopkins University School of Medicine, Baltimore, Md.

Meijo University, Nagoya, Japan

Pierre and Marie Curie University, Paris, France

Tethered capsule endomicroscopy

By Tracey Baas, Senior Editor

Massachusetts General Hospital researchers have created a new kind of endoscopy device that resembles a large plastic vitamin capsule on a tether and can generate 3D microstructural images of the upper GI tract.¹ As proof of concept, the team used the device to image Barrett's esophagus in patients. The technology is licensed to **NinePoint Medical Inc.**

Recurrent acid reflux, which usually presents as heartburn, can lead to cells in the epithelium of the lower esophagus being replaced with GI-like cells and abnormal microstructure. This condition is diagnosed as Barrett's esophagus and can progress from dysplasia to esophageal cancer.²

To diagnose Barrett's esophagus, the current standard is a method called endoscopic biopsy, during which doctors sedate a patient, insert an endoscope down the esophagus to look for abnormal tissue and then cut off a small piece of the organ for laboratory analysis—this leaves the patient with a sore throat for the next couple of days.

An alternative method is to use a capsule endoscope, which is a clear plastic pill that contains a video camera. The pill is swallowed by the patient and takes images of the GI tract.

There is one capsule endoscope on the market to image the esophagus—the PillCam ESO from **Given Imaging Ltd.** The product houses two cameras—one at each end—that are capable of

acquiring 14 images per second.³

Unlike a full endoscope procedure, however, the video imaging can only provide information about superficial mucosal structures and not microscopic features below the tissue surface. Thus, histological diagnosis of Barrett's esophagus is not possible.

Instead, PillCam ESO gives a diagnosis of endoscopic suspicion of esophageal metaplasia.^{4,5} Patients who test positive for that typically undergo an actual endoscope procedure to identify lesions and collect biopsies to evaluate for dysplasia.

The MGH team, led by Guillermo Tearney, wanted to overcome the resolution problems intrinsic to video imaging. To do so, the group engineered a capsule that captures snapshots with optical frequency domain imaging (OFDI), a technique that is similar to ultrasound. The pill performs more like a microscope than a video camera.

The snapshots can then be put together—computationally stacking the data collected from the OFDI—to reconstruct a 3D image of the esophagus and provide enough detail and depth to allow the diagnosis of abnormal growth patterns in esophageal tissue.

Tearney is a professor of pathology at **Harvard Medical School**, MGH research scholar and associate director of the Wellman Center for Photomedicine at MGH.

The team's first step was slowing down the transit of the capsule in the esophagus to allow it to collect enough snapshots to produce a 3D representation of the esophagus. The group placed the capsule on a tether, which enabled the operator to move the capsule up and down, thus allowing for multiple passes in the esophagus.

As proof of concept, the tethered capsule collected images in six individuals with Barrett's esophagus and seven healthy individuals. The image collection time took about six minutes, and after the procedure the capsule could be recovered, disinfected and reused.

The technology showed clear evidence of Barrett's in those with the disease, whereas those without Barrett's had a normal scan.

"This is not the first time either a tethered capsule or OFDI has been used to attempt to diagnose Barrett's, but using the two techniques together, this is the first time accurate diagnosis can be made using a fairly noninvasive technique," said Tearney.⁶⁻¹⁰

Results were published in *Nature Medicine*.

Getting to the NinePoint

NinePoint plans to optimize the tethered capsule technology and run imaging and diagnostic trials in larger sets of patients.

Marc Schurr thinks that "the imaging contrast seems appropriate to be used for diagnostics, but clinical trials with an appropriate number of cases will be needed to establish specificity and sensitivity of the procedure."

Schurr is managing director of **novineon Healthcare Technology Partners GmbH** and leader of a consortium of 18 European teams working on the VECTOR (versatile endoscopic capsule for gastrointestinal tumor recognition and therapy) project.

NinePoint thinks that capsule endoscopy, after optimization, could be used throughout the GI tract to obtain information about diseases of the esophagus, stomach and upper small bowel.

"We will be focusing first on the esophagus because it is the easier site to image in the GI tract," said Tearney, who is a consultant to NinePoint.

"The technique also could be used to assess inflammatory diseases of the esophagus, squamous cell cancer and its precursors and changes in the small bowel related to celiac disease," said Charles Carignan, founding president and CEO of NinePoint. "If we were able to create a wireless device that does not require the tether, the device could have additional applicability in the lower small bowel and possibly colon."

"In the near future, we are most interested in improving the capsule by adding controlled locomotion and video imaging for guidance," he noted.

This would give greater control in GI sites downstream of the esophagus.

A patent application has been filed by MGH, and NinePoint has licensed the technology.

NinePoint's lead product is a balloon-based optical coherence tomography system that can be used through existing endoscopes to image microstructures of organs such as the esophagus and identify areas for biopsy and treatment. It is the same technology underlying the tethered capsule. This technology, which originated in Tearney's and Brett Bouma's lab, will be commercialized this year.

Bouma is a professor of dermatology and health sciences and technology at HMS and an associate physicist at the Wellman Center for Photomedicine at MGH.

"The technique also could be used to assess inflammatory diseases of the esophagus, such as squamous cell cancer and its precursors, and assess changes in the small bowel related to celiac disease."

—Charles Carignan,
NinePoint Medical Inc.

NinePoint also has licensed rights to a volumetric confocal technology from MGH that allows imaging of mucosa at a cellular level. This technology could be developed in a balloon- or capsule-based method to allow characterization of mucosal abnormalities in the body, such as eosinophilic esophagitis.

Baas, T. *SciBX* 6(6); doi:10.1038/scibx.2013.131

Published online Feb. 14, 2013

REFERENCES

1. Gora, M.J. *et al. Nat. Med.*; published online Jan. 13, 2013; doi:10.1038/nm.3052
Contact: Guillermo Tearney, Massachusetts General Hospital and Harvard Medical School, Boston, Mass.
e-mail: gtearney@partners.org
2. Reid, B.J. *et al. Nat. Rev. Cancer* 10, 87–101 (2010)

3. Moglia, A. *et al. Nat. Rev. Gastroenterol. Hepatol.* 6, 353–362 (2009)
4. Galmiche, J.P. *et al. Gut* 57, 695–703 (2008)
5. Vakil, N. *et al. Am. J. Gastroenterol.* 101, 1900–1920 (2006)
6. Evans, J.A. *et al. Gastrointest. Endosc.* 65, 50–56 (2007)
7. Evans, J.A. *et al. Clin. Gastroenterol. Hepatol.* 4, 38–43 (2006)
8. Poneros, J.M. *et al. Gastroenterology* 120, 7–12 (2001)
9. Ramirez, F.C. *et al. Gastrointest. Endosc.* 68, 25–31 (2008)
10. Gilani, N. *et al. Gastrointest. Endosc.* 66, 1091–1095 (2007)

COMPANIES AND INSTITUTIONS MENTIONED

Given Imaging Ltd. (NASDAQ:GIVN; Tel Aviv:GIVN), Yoqneam, Israel
Harvard Medical School, Boston, Mass.
Massachusetts General Hospital, Boston, Mass.
NinePoint Medical Inc., Cambridge, Mass.
novineon Healthcare Technology Partners GmbH, Tuebingen, Germany

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

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				
Breast cancer	MicroRNA-374a (miR-374a)	<p>Patient sample and mouse studies suggest inhibiting miR-374a could help prevent or treat breast cancer metastasis. In a mouse xenograft model for breast cancer, cells that overexpressed miR-374a caused greater metastasis than cells that expressed normal levels of miR-374a. In cells that expressed normal levels of miR-374a, antagomir-mediated knockdown of miR-374a expression led to less metastasis than no knockdown. Primary tumor samples from breast cancer patients with disease metastasis showed higher miR-374a expression than samples from patients without metastases. Next steps include optimizing the miR-374a antagomir.</p> <p>SciBX 6(6); doi:10.1038/scibx.2013.132 Published online Feb. 14, 2013</p>	Patent application filed; available for licensing	<p>Cai, J. <i>et al. J. Clin. Invest.</i>; published online Jan. 16, 2013; doi:10.1172/JCI65871 Contact: Mengfeng Li, Sun Yat-Sen University, Guangzhou, China e-mail: limf@mail.sysu.edu.cn</p>
Cancer	BCL2-associated X protein (BAX); BCL2-antagonist/killer 1 (BAK1; BAK); B cell lymphoma 2 (BCL-2; BCL2); BCL3 homology domain 3 (BH3)	<p>Structural studies have identified regions of BAX and BAK that could guide the development of a new class of BH3-mimetic drugs that directly trigger apoptosis and help treat cancer. Crystal structures of BCL2 have guided the development of BH3-mimetic compounds that bind and inhibit prosurvival proteins; however, it was unclear how BH3 domains bind and activate proapoptotic proteins, such as BAX and BAK. <i>In vitro</i> and crystallographic studies of BAX in complex with BH3 peptides have now identified domains on the protein's surface necessary for BH3-driven oligomerization and activation that triggers apoptosis. Next steps could include developing BH3-mimetic compounds that directly bind BAX and trigger or block apoptosis. Abbott Laboratories and Roche's Genentech Inc. have navitoclax (ABT-263), a pan-inhibitor of BCL2-family proteins, in Phase I/II testing in small cell lung cancer and Phase I testing in additional cancers. At least six additional companies have antagonists of BCL2 family proteins in development stages from preclinical to Phase II testing for cancer.</p> <p>SciBX 6(6); doi:10.1038/scibx.2013.133 Published online Feb. 14, 2013</p>	Patent status undisclosed; available for licensing	<p>Czabotar, P.E. <i>et al. Cell</i>; published online Jan. 31, 2013; doi:10.1016/j.cell.2012.12.031 Contact: Peter M. Colman, The Walter and Eliza Hall Institute of Medical Research, Melbourne, Victoria, Australia e-mail: pcolman@wehi.edu.au Contact: Peter E. Czabotar, same affiliation as above e-mail: czabotar@wehi.edu.au</p>
Cancer	Prominin 1 (PROM1; CD133)	<p>Mouse studies suggest oncolytic measles viruses engineered to target CD133 could help treat cancer. CD133 is a marker of stem cells and is highly expressed in many cancers. In mice bearing CD133-expressing human hepatocellular carcinoma, a CD133-targeted oncolytic measles virus decreased tumor growth and increased survival compared with a nontargeted measles virus. Next steps include testing the strain in additional tumor types and developing viruses that target additional tumor markers.</p> <p>SciBX 6(6); doi:10.1038/scibx.2013.134 Published online Feb. 14, 2013</p>	Patent and licensing status undisclosed	<p>Bach, P. <i>et al. Cancer Res.</i>; published online Jan. 4, 2013; doi:10.1158/0008-5472.CAN-12-2221 Contact: Christian J. Buchholz, Paul Ehrlich Institute, Langen, Germany e-mail: christian.buchholz@pei.de</p>

This week in therapeutics (continued)

Indication	Target/marker/pathway	Summary	Licensing status	Publication and contact information
Cancer	Ras homolog gene family member A (RHOA); leukemia-associated Rho guanine nucleotide exchange factor (LARG)	<i>In vitro</i> studies identified a small molecule inhibitor of the interaction between LARG and RHOA that could help treat cancers. In human fibroblasts, a compound designed to specifically block the RHOA binding site on LARG inhibited RHOA activity and disrupted actin cytoskeletal organization and adhesion. In human breast cancer cells, the compound inhibited growth, migration, invasion and mammary sphere formation at double-digit micromolar concentrations. Next steps include identifying improved lead compounds for clinical testing. SciBX 6(6); doi:10.1038/scibx.2013.135 Published online Feb. 14, 2013	Patent application filed; available for licensing	Shang, X. <i>et al. Proc. Natl. Acad. Sci. USA</i> ; published online Feb. 4, 2013; doi:10.1073/pnas.1212324110 Contact: Yi Zheng, Children's Hospital Medical Center, Cincinnati, Ohio e-mail: yi.zheng@cchmc.org
Melanoma	BRAF	A study in mice suggests intermittent rather than continuous dosing of Zelboraf could prevent or delay drug resistance in patients with melanoma. In xenograft mice implanted with subcutaneous melanoma tumors, intermittent dosing of the small molecule BRAF inhibitor Zelboraf did not lead to drug resistance in any animals after 200 days, whereas continuous dosing of the drug led to lethal Zelboraf resistance within 100 days. Next steps include testing the intermittent dosing regimen in patients with melanoma. Zelboraf vemurafenib (PLX4032) is marketed by Roche and Daiichi Sankyo Co. Ltd. to treat metastatic melanoma in patients expressing the V600E BRAF mutation. Dabrafenib (GSK2118436), a small molecule BRAF inhibitor from GlaxoSmithKline plc, is in registration to treat advanced or metastatic BRAF mutant melanoma. SciBX 6(6); doi:10.1038/scibx.2013.136 Published online Feb. 14, 2013	Patent and licensing status undisclosed	Das Thakur, M. <i>et al. Nature</i> ; published online Jan. 9, 2013; doi:10.1038/nature11814 Contact: Darrin D. Stuart, Novartis Institutes for BioMedical Research, Emeryville, Calif. e-mail: darrin.stuart@novartis.com Contact: Martin McMahon, University of California, San Francisco, Calif. e-mail: mcmahon@cc.ucsf.edu
Non-small cell lung cancer (NSCLC)	Angiotensinogen (AGT); angiotensin-converting enzyme (ACE)	Patient tissue and mouse studies suggest ACE inhibitors could help treat NSCLC in patients with angiotensin II-overexpressing tumors. In a histological analysis of biopsies from 44 patients with NSCLC, 16 showed increased expression of the angiotensin II precursor AGT. In a genetic mouse model for NSCLC, the ACE inhibitor Vaseretic enalapril, which inhibits AGT cleavage and angiotensin II production, slowed tumor progression and increased survival compared with a control compound. Next steps include testing enalapril in combination with cancer therapeutics and investigating the mechanisms of enalapril resistance. Vaseretic enalapril is marketed by Merck & Co. Inc. to treat hypertension and congestive heart failure (CHF). SciBX 6(6); doi:10.1038/scibx.2013.137 Published online Feb. 14, 2013	Unpatented; licensing status not applicable	Cortez-Retamozo, V. <i>et al. Immunity</i> ; published online Jan. 17, 2013; doi:10.1016/j.immuni.2012.10.015 Contact: Mikael J. Pittet, Massachusetts General Hospital, Boston, Mass. e-mail: mpittet@mgh.harvard.edu
Non-small cell lung cancer (NSCLC)	Serine/threonine kinase 11 (STK11; LKB1); <i>K-Ras</i>	Mouse and cell culture studies suggest the metformin analog phenformin could help treat <i>K-Ras</i> -driven NSCLCs with <i>LKB1</i> mutations. In an <i>LKB1</i> -deficient human NSCLC cell line, phenformin induced apoptosis, whereas metformin did not. In mice bearing <i>K-Ras</i> -driven <i>Lkb1</i> -deficient NSCLC tumors, oral phenformin led to lower tumor burden and greater survival than vehicle. Next steps could include testing phenformin in additional models of <i>LKB1</i> -deficient cancers. Metformin is a generic drug approved to treat diabetes and is in clinical testing to treat various cancers. Phenformin was previously marketed to treat diabetes but was withdrawn by the FDA in 1978 due to toxicity. SciBX 6(6); doi:10.1038/scibx.2013.138 Published online Feb. 14, 2013	Patent and licensing status unavailable	Shackelford, D.B. <i>et al. Cancer Cell</i> ; published online Jan. 24, 2013; doi:10.1016/j.ccr.2012.12.008 Contact: Reuben J. Shaw, Salk Institute for Biological Studies, La Jolla, Calif. e-mail: shaw@salk.edu Contact: David B. Shackelford, same affiliation as above e-mail: dshackelford@mednet.ucla.edu

This week in therapeutics (continued)

Indication	Target/marker/ pathway	Summary	Licensing status	Publication and contact information
Endocrine/metabolic disease				
Diabetes	Unknown	<p>Cell culture and mouse studies suggest a diarylurea-based compound could help regenerate β cell mass and treat type 1 diabetes. In an islet proliferation assay, the compound increased proliferation of primary rat and human islets compared with vehicle. In a mouse model for β cell ablation, the compound increased β cell mass and decreased blood glucose levels compared with vehicle. Next steps include efficacy studies in the nonobese diabetic mice.</p> <p>SciBX 6(6); doi:10.1038/scibx.2013.139 Published online Feb. 14, 2013</p>	Patent application filed; unlicensed	<p>Shen, W. <i>et al. J. Am. Chem. Soc.</i>; published online Jan. 19, 2013; doi:10.1021/ja309304m</p> <p>Contact: Peter G. Schultz, The Scripps Research Institute, La Jolla, Calif. e-mail: schultz@scripps.edu</p> <p>Contact: Richard Glynne, The Genomics Institute of the Novartis Research Foundation, San Diego, Calif. e-mail: rglynne@gnf.org</p>
Genitourinary disease				
Benign prostatic hyperplasia (BPH)	Gastrin-releasing peptide (GRP)	<p><i>In vitro</i> and rat studies suggest GRP antagonists could help treat BPH. In human prostate cell lines, a GRP antagonist decreased cell proliferation compared with no treatment. In rat models of testosterone-induced BPH, the GRP antagonist decreased prostate size and inflammatory markers compared with no treatment. Next steps could include studying GRP antagonists in additional animal models of BPH.</p> <p>SciBX 6(6); doi:10.1038/scibx.2013.140 Published online Feb. 14, 2013</p>	Findings unpatented; licensing status not applicable	<p>Rick, F.G. <i>et al. Proc. Natl. Acad. Sci. USA</i>; published online Jan. 28, 2013; doi:10.1073/pnas.1222355110</p> <p>Contact: Andrew V. Schally, Veterans Affairs Medical Center and University of Miami Miller School of Medicine, Miami, Fla. e-mail: andrew.schally@va.gov</p> <p>Contact: Ferenc G. Rick, Veterans Affairs Medical Center, Miami, Fla. e-mail: ferencrick@gmail.com</p>
Inflammation				
Inflammation	Adrenergic receptor α_2 (ADRA2)	<p>Rat studies suggest ADRA2 agonists could help reduce fevers. In rats, injection of the ADRA2 agonist clonidine in the brain inhibited thermogenesis. Also in rats, intraperitoneal injection of the ADRA2 agonist Precedex dexmedetomidine decreased lipopolysaccharide (LPS)-induced fever compared with saline injection. Next steps include determining whether ADRA2 agonists could be dosed at a level that reduces fever without also causing known cardiovascular side effects. Orion Corp., Abbott Laboratories and Hospira Inc. market Precedex as a sedative. Clonidine is a generic antihypertensive drug.</p> <p>SciBX 6(6); doi:10.1038/scibx.2013.141 Published online Feb. 14, 2013</p>	Patent and licensing status undisclosed	<p>Madden, C.J. <i>et al. J. Neurosci.</i>; published online Jan. 30, 2013; doi:10.1523/JNEUROSCI.4701-12.2013</p> <p>Contact: Christopher J. Madden, Oregon Health & Science University, Portland, Ore. e-mail: maddench@ohsu.edu</p>
Inflammation	Elastase	<p><i>In vitro</i> studies identified elastase inhibitors that could help treat inflammation. In enzymatic assays, marine cyanobacterium-derived molecules called symprostins inhibited human neutrophil elastase (NE; ELA-2) with potency comparable to that of the marketed inhibitor sivelestat. In bronchial epithelial cells, the lead compound prevented elastase-induced inflammation with potency comparable to that of sivelestat. Next steps could include further optimization of the new compounds for <i>in vivo</i> testing. Ono Pharmaceutical Co. Ltd. markets sivelestat to treat acute lung injury.</p> <p>SciBX 6(6); doi:10.1038/scibx.2013.142 Published online Feb. 14, 2013</p>	Patent and licensing status unavailable	<p>Salvador, L.A. <i>et al. J. Med. Chem.</i>; published online Jan. 28, 2013; doi:10.1021/jm3017305</p> <p>Contact: Hendrik Luesch, University of Florida, Gainesville, Fla. e-mail: luesch@cop.ufl.edu</p>

This week in therapeutics (continued)

Indication	Target/marker/ pathway	Summary	Licensing status	Publication and contact information
Neurology				
Depression; anxiety	Dopamine signaling	<p>Mouse studies suggest blocking neurotransmission of dopamine-sensing neurons could help treat neuropsychiatric disorders triggered by chronic stress. In wild-type mice subjected to chronic stress–inducing social defeat, the generic small molecule quinpirole decreased the activity of dopamine-sensing neurons and led to increased social interaction compared with vehicle control. Next steps include developing compounds that selectively target dopamine signaling to treat neuropsychiatric disorders (see Stressing out over depression and anxiety, page 5).</p> <p>SciBX 6(6); doi:10.1038/scibx.2013.143 Published online Feb. 14, 2013</p>	Unpatented; unavailable for licensing	<p>Barik, J. <i>et al. Science</i>; published online Jan. 18, 2013; doi:10.1126/science.1226767 Contact: François Tronche, Pierre and Marie Curie University, Paris, France e-mail: francois.tronche@upmc.fr Contact: Jacques Barik, same affiliation as above e-mail: jacques.barik@snv.jussieu.fr</p>
Depression; anxiety	Glucocorticoid receptor (GCCR); <i>disrupted in schizophrenia 1</i> (DISC1)	<p>Mouse studies suggest blocking the glucocorticoid receptor in the brain could help treat adult-onset neuropsychiatric disorders triggered by adolescent stress. In adolescent transgenic mice expressing depression-associated DISC1 and subjected to three weeks of isolation stress, a small molecule GCCR antagonist decreased depressive-like social behavior compared with vehicle control. The behavioral improvements were associated with normalized DNA methylation of the promoter of <i>tyrosine hydroxylase</i> (TH; TYH), which is part of the biosynthetic pathway of the neurotransmitter dopamine. Next steps include looking for additional epigenetic modifications that may occur following prolonged adolescent stress (see Stressing out over depression and anxiety, page 5).</p> <p>SciBX 6(6); doi:10.1038/scibx.2013.144 Published online Feb. 14, 2013</p>	Unpatented; unavailable for licensing	<p>Niwa, N. <i>et al. Science</i>; published online Jan. 18, 2013; doi:10.1126/science.1226931 Contact: Akira Sawa, The Johns Hopkins University School of Medicine, Baltimore, Md. e-mail: asawa1@jhmi.edu Contact: Toshitaka Nabeshima, Meijo University, Nagoya, Japan e-mail: tnabeshi@meijo-u.ac.jp</p>
Fragile X syndrome	Ras; MAP kinase 3 (MAPK3; ERK-1); MAPK1 (ERK-2)	<p>Studies in mice suggest lovastatin could help treat epilepsy in patients with fragile X syndrome. In hippocampus slices from a mouse model for fragile X syndrome, lovastatin decreased Ras-ERK-1/ERK-2 pathway signaling, abnormally high protein synthesis and epilepsy-associated activity bursts compared with vehicle. Lovastatin also decreased seizures. Next steps include dose ranging studies and developmental timing studies to identify a therapeutic window for statin treatment in patients with fragile X syndrome. The generic lovastatin is an HMG-CoA reductase inhibitor marketed to treat dyslipidemia and coronary artery disease (CAD). Seaside Therapeutics Inc.'s arbaclofen (STX-209), a GABA_B receptor antagonist, is in Phase III testing for fragile X syndrome. Novartis AG's AFQ056, a metabotropic glutamate receptor subtype 5 (mGluR5; GRM5) antagonist, is in Phase III trials for fragile X syndrome (see Statins for fragile X, page 4).</p> <p>SciBX 6(6); doi:10.1038/scibx.2013.145 Published online Feb. 14, 2013</p>	Patent pending; available for licensing	<p>Osterweil, E.K. <i>et al. Neuron</i>; published online Jan. 23, 2013; doi:10.1016/j.neuron.2012.01.034 Contact: Mark F. Bear, Massachusetts Institute of Technology, Cambridge, Mass. e-mail: mbear@mit.edu</p>

This week in techniques

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

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

Approach	Summary	Licensing status	Publication and contact information
Assays & screens			
High throughput small hairpin RNA-based genetic interaction mapping in human cells	<p>A high throughput method to analyze genetic interactions in human cells could help identify new disease pathways and targets. A library of shRNAs was synthesized against all annotated human protein-coding genes that carried, on average, 25 independent shRNAs per target. In cultured human cells treated with the library, quantification of shRNA levels by deep sequencing identified shRNAs against a series of targets, including HMG-CoA reductase, which decreased ricin toxicity compared with control shRNA. In a secondary screen of positive shRNA hits, a library containing every pairwise combination of two shRNAs identified synergistic or suppressive genetic interactions, which led to the identification of multiple putative protein pathways or complexes that affect ricin sensitivity. Next steps include using the method to analyze genetic interactions in cancer cells.</p> <p>SciBX 6(6); doi:10.1038/scibx.2013.146 Published online Feb. 14, 2013</p>	Patent and licensing status undisclosed	<p>Bassik, M.C. <i>et al. Cell</i>; published online Feb. 7, 2013; doi:10.1016/j.cell.2013.01.030 Contact: Martin Kampmann University of California, San Francisco, Calif. e-mail: martin.kampmann@ucsf.edu Contact: Michael C. Bassik, same affiliation as above e-mail: bassik@cmp.ucsf.edu</p>
Protein translocation through an α -hemolysin-caseinolytic peptidase X homolog (ClpX) nanopore system	<p>A method to translocate proteins through α-hemolysin nanopores could eventually enable nanopore-based protein sequencing. There are nanopore-based DNA sequencing methods in commercial development that detect and identify DNA by measuring voltage changes as individual base pairs pass through a membrane-embedded nanopore, but these methods cannot identify peptides. To enable protein translocation through a membrane-embedded nanopore, the AAA⁺ unfoldase ClpX was added in solution to one side of the membrane, allowing detection of structure-dependent voltage changes as a protein substrate of about 100 amino acids and carrying a ClpX binding tag passed through the pore. Next steps could include determining the relationship between voltage change and amino acid identity.</p> <p>At least five companies are developing nanopore-based DNA sequencing systems.</p> <p>SciBX 6(6); doi:10.1038/scibx.2013.147 Published online Feb. 14, 2013</p>	Patent and licensing status undisclosed	<p>Nivala, J. <i>et al. Nat. Biotechnol.</i>; published online Feb. 3, 2013; doi:10.1038/nbt.2503 Contact: Mark Akeson, University of California, Santa Cruz, Calif. e-mail: makeson@soe.ucsc.edu</p>
Sensitizing bacteria to antibiotics by increasing reactive oxygen species (ROS) production	<p><i>In silico</i> prediction and <i>in vitro</i> screening could help identify targets that increase bacterial ROS production and improve the efficacy of marketed antibiotics. A workflow was developed that included computational modeling of the metabolic state of <i>Escherichia coli</i> followed by <i>in vitro</i> validation of gene targets that could modulate ROS production. <i>In vitro</i>, knockout strains predicted to have increased ROS production showed greater sensitivity to the generic antibiotics ampicillin and ofloxacin than control strains. Next steps could include using this approach to screen for ROS-inducing compounds to use in combination with antibiotics.</p> <p>SciBX 6(6); doi:10.1038/scibx.2013.148 Published online Feb. 14, 2013</p>	Patent application filed; licensed to EnBiotix Inc.	<p>Brynildsen, M.P. <i>et al. Nat. Biotechnol.</i>; published online Jan. 6, 2013; doi:10.1038/nbt.2458 Contact: James J. Collins, Boston University, Boston, Mass. e-mail: jcollins@bu.edu</p>
Chemistry			
Anti-amyloid compounds that inhibit biofilm formation	<p><i>In vitro</i> studies suggest compounds that disrupt amyloid fibers could be useful for preventing biofilm formation. In a cell culture assay of biofilm formation by the commensal bacterium <i>Bacillus subtilis</i>, the benzoquinone AA-861 and the lactone parthenolide prevented biofilm formation. <i>In vitro</i>, the two compounds blocked amyloid formation by a variety of amyloid-forming proteins. Next steps could include optimizing and testing hit compounds for inhibition of biofilms formed by pathogenic bacteria.</p> <p>SciBX 6(6); doi:10.1038/scibx.2013.149 Published online Feb. 14, 2013</p>	Patent and licensing status unavailable	<p>Romero, D. <i>et al. Chem. Biol.</i>; published online Jan. 24, 2013; doi:10.1016/j.chembiol.2012.10.021 Contact: Roberto Kolter, Harvard Medical School, Boston, Mass. e-mail: rkolter@hms.harvard.edu</p>

This week in techniques (continued)

Approach	Summary	Licensing status	Publication and contact information
Computational models			
Computational approach for prioritizing potential cancer targets	<p>A computational approach that predicts the druggability of cancer-associated proteins could help prioritize targets in small molecule discovery programs. The computational approach integrates target class, bioactivity data, protein structural information and homology modeling to estimate a protein's druggability. From a list of 479 genes known to be altered in cancer, the method identified 29 oncogenes and 16 tumor suppressors predicted to be druggable but for which few or no small molecule ligands had yet been reported. Next steps include incorporating additional cancer genomic data and could include prioritizing additional types of gene lists such as those from synthetic lethal screens in cancer cell lines. The computational method is freely available through the canSAR database hosted by The Institute of Cancer Research (<i>see Cancer target selection pressure</i>, page 1).</p> <p>SciBX 6(6); doi:10.1038/scibx.2013.150 Published online Feb. 14, 2013</p>	Unpatented; licensing status not applicable	<p>Patel, M.N. <i>et al. Nat. Rev. Drug Discov.</i>; published online Dec. 31, 2012; doi:10.1038/nrd3913 Contact: Bissan Al-Lazikani, The Institute of Cancer Research, London, U.K. e-mail: bissan.al-lazikani@icr.ac.uk Contact: Paul Workman, same affiliation as above e-mail: paul.workman@icr.ac.uk</p>
Disease models			
Patient induced pluripotent stem (iPS) cell-derived cardiomyocytes as models for right ventricular dysplasia/cardiomyopathy	<p>Cardiomyocytes generated from patient-derived iPS cells could help identify new treatments for right ventricular dysplasia/cardiomyopathy. Fibroblasts were isolated from an adult patient, reprogrammed into iPS cells and subsequently differentiated into cardiomyocytes. In culture, the resulting cells recapitulated an adult cardiomyocyte phenotype, showing exaggerated lipogenesis and deficiencies in calcium handling and greater apoptosis than control cells. Next steps include extending the findings to additional subtypes of right ventricular dysplasia/cardiomyopathy and using the patient-derived cells to evaluate therapeutic candidates.</p> <p>SciBX 6(6); doi:10.1038/scibx.2013.151 Published online Feb. 14, 2013</p>	Patents pending; licensing status undisclosed	<p>Kim, C. <i>et al. Nature</i>; published online Jan. 27, 2013; doi:10.1038/nature11799 Contact: Huei-Sheng Vincent Chen, Sanford-Burnham Medical Research Institute, La Jolla, Calif. e-mail: hsv_chen@burnham.org</p>
Drug delivery			
Adjuvant and antigen co-delivery with nickel-chelating lipid nanoparticles	<p>Nickel-chelating lipid nanoparticles that co-deliver antigens and adjuvants could be useful for vaccine delivery. Nickel-chelating lipid nanoparticles were formulated to carry the adjuvants monophosphoryl lipid A or cholesterol-modified CpG oligodeoxynucleotides and histidine-tagged recombinant viral or bacterial antigens. In mice, injection of the particles resulted in fivefold to sevenfold higher antibody titers than co-delivery of adjuvant and antigen as separate entities. Next steps could include testing the efficacy of the lipid nanoparticles in mouse models for viral and bacterial infection.</p> <p>SciBX 6(6); doi:10.1038/scibx.2013.152 Published online Feb. 14, 2013</p>	Patent and licensing status unavailable	<p>Fischer, N.O. <i>et al. J. Am. Chem. Soc.</i>; published online Jan. 18, 2013; doi:10.1021/ja3063293 Contact: Craig D. Blanchette, Lawrence Livermore National Laboratory, Livermore, Calif. e-mail: blanchette2@llnl.gov Contact: Paul D. Hoeprieh, same affiliation as above e-mail: hoeprieh2@llnl.gov</p>
Dissolving microneedle arrays for delivery of live adenovirus vaccines	<p>A dissolvable microneedle array could be used for transdermal delivery of adenovirus vaccines. Recombinant human adenovirus type 5 vectors expressing chicken ovalbumin or HIV gag polyprotein antigens were formulated as a dry powder and incorporated into the matrix of a dissolvable microneedle array. In mice, skin immunization using the microneedle array led to antigen-specific CD8⁺ T cell responses that were comparable to those induced by conventional injection routes for vaccine delivery. Next steps include testing the microneedle arrays on cadaver skin and then in clinical trials. TheraJect Inc. was involved in the study and has the dissolving microneedle arrays in preclinical development to deliver therapeutics and vaccines.</p> <p>SciBX 6(6); doi:10.1038/scibx.2013.153 Published online Feb. 14, 2013</p>	Microneedle array covered by multiple issued and pending patents; available for licensing from TheraJect	<p>Bachy, V. <i>et al. Proc. Natl. Acad. Sci. USA</i>; published online Feb. 5, 2013; doi:10.1073/pnas.1214449110 Contact: Linda S. Klavinskis, King's College London School of Medicine, London, U.K. e-mail: linda.klavinskis@kcl.ac.uk</p>

This week in techniques (continued)

Approach	Summary	Licensing status	Publication and contact information
Markers			
Highly prevalent <i>telomerase reverse transcriptase (TERT)</i> promoter mutations in melanoma	<p>Two independent studies identified highly prevalent mutations upstream of <i>TERT</i> that could help guide the development of new treatments for melanoma. In a family with members diagnosed with melanoma, sequencing studies identified mutations upstream of <i>TERT</i> in all affected individuals. In sporadic melanoma cases, one study identified mutations upstream of <i>TERT</i> in 33% of primary tumors and 85% of metastatic tumors, whereas the second study identified mutations upstream of <i>TERT</i> in 71% of melanoma samples. In cells carrying the mutations, <i>TERT</i> expression was greater than that in cells without such mutations. Next steps include additional studies evaluating the functional consequences of these mutations and the effect of <i>TERT</i> inhibition in this population.</p> <p>SciBX 6(6); doi:10.1038/scibx.2013.154 Published online Feb. 14, 2013</p>	Findings in both studies unpatented; licensing status not applicable	<p>Huang, F.W. <i>et al. Science</i>; published online Jan. 24, 2013; doi:10.1126/science.1229259 Contact: Levi A. Garraway, Broad Institute of MIT and Harvard, Cambridge, Mass. e-mail: levi_garraway@dfci.harvard.edu</p> <p>Horn, S. <i>et al. Science</i>; published online Jan. 24, 2013; doi:10.1126/science.1230062 Contact: Rajiv Kumar, German Cancer Research Center, Heidelberg, Germany e-mail: r.kumar@dkfz.de Contact: Susanne Horn, same affiliation as above e-mail: s.horn@dkfz.de Contact: Dirk Schadendorf, Essen University Hospital, Essen, Germany e-mail: dirk.schadendorf@uk-essen.de</p>



SciBX: Science-Business eXchange

“Understanding the business context and commercial relevance of new science is the key to lowering investment risk and stimulating industry innovation”

Become a Charter Subscriber today!

Visit scibx.com for details on the special SciBX Charter Subscriber Offer

Company and institution index

A	
Abbott Laboratories	9,11
Afraxis Inc.	4
C	
Cancer Research UK	1
D	
Daiichi Sankyo Co. Ltd.	10
E	
EnBiotix Inc.	13
G	
Genentech Inc.	5,9
Given Imaging Ltd.	7
GlaxoSmithKline plc	3,10
H	
Harvard Medical School	7
Hospira Inc.	11
Howard Hughes Medical Institute	4
I	
Institute of Cancer Research	1,14
J	
Johns Hopkins University School of Medicine	6
M	
Massachusetts General Hospital	7
Massachusetts Institute of Technology	4
Meijo University	6
Merck & Co. Inc.	1,10
N	
NinePoint Medical Inc.	7
Novartis AG	4,12
novineon Healthcare Technology Partners GmbH	7
O	
Ono Pharmaceutical Co. Ltd.	11
Orion Corp.	11
P	
Pierre and Marie Curie University	5
R	
Roche	4,9,10

S	
Sage Bionetworks	1
Seaside Therapeutics Inc.	4,12
T	
TheraJect Inc.	14
U	
University of North Carolina at Chapel Hill Eshelman School of Pharmacy	2
.....	

Target and compound index

A	
α -Hemolysin	13
AA-861	13
ABT-263	9
ACE	10
ADRA2	11
Adrenergic receptor α_2	11
AFQ056	4,12
AGT	10
Ampicillin	13
Angiotensin-converting enzyme	10
Angiotensin II	10
Angiotensinogen	10
Arbaclofen	4,12
B	
BAK	9
BAK1	9
BAX	9
B cell lymphoma 2	9
BCL-2	9
BCL2	9
BCL2-antagonist/killer 1	9
BCL2-associated X protein	9
BCL3 homology domain 3	9
BH3	9
BRAF	10
C	
Caseinolytic peptidase X homolog	13
CD8	14
CD133	9
Cholesterol	4
Clonidine	11
ClpX	13
Cocaine	5
Corticosterone	6
CpG oligodeoxynucleotide	14

D	
Dabrafenib	10
Dexmedetomidine	11
Diarylurea	11
DISC1	5,12
Disrupted in schizophrenia 1	5,12
Dopamine	5,12
E	
ELA-2	11
Elastase	11
Enalapril	10
ERK-1	4,12
ERK-2	4,12
F	
FMR1	4
Fragile X mental retardation 1	4
G	
GABA _B receptor	4,12
Gastrin-releasing peptide	11
GCCR	5,12
Glucocorticoid	5
Glucocorticoid receptor	5,12
GRM5	4,12
GRP	11
GSK2118436	10
H	
Histone acetyltransferase	3
HIV gag polyprotein	14
HMG-CoA reductase	4,12,13
K	
K-Ras	10
L	
L3MBTL3	3
LARG	10
Leukemia-associated Rho guanine nucleotide exchange factor	10
Lipopolysaccharide	11
LKB1	10
Lovastatin	4,12
LPS	11
ι (3)Mbt-like 3	3
M	
MAPK1	4,12
MAPK3	4,12
MAP kinase 3	4,12
Metabotropic glutamate receptor subtype 5	4,12
Metformin	10
Methyllysine	3
mGluR5	4,12

MicroRNA-374a	9
miR-374a	9
Monophosphoryl lipid A	14
N	
Navitoclax	9
NE	11
Neutrophil elastase	11
O	
Ofloxacin	13
Ovalbumin	14
P	
p21 protein (Cdc42 Rac)-activated kinase 1	4
PAK1	4
Parthenolide	13
Phenformin	10
PillCam ESO	7
PLX4032	10
Precedex	11
PROM1	9
Prominin 1	9
Q	
Quinpirole	5,12
R	
Ras	4,12
Ras homolog gene family member A	10
Reactive oxygen species	13
RG7090	4
RHOA	10
ROS	13
S	
Serine/threonine kinase 11	10
Sivilestat	11
STK11	10
STX-107	4
STX-209	4,12
Symplostatin	11
T	
Telomerase reverse transcriptase	15
TERT	15
TH	6,12
TYH	6,12
Tyrosine hydroxylase	6,12
V	
Vaseretic	10
Vemurafenib	10
Z	
Zelboraf	10