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By *Tim Fulmer, Senior Writer*

A team of NIH researchers has linked phosphoinositide 3-kinase- $\delta$  to neuregulin signaling and shown that inhibiting the kinase improved behavior in rodent models of schizophrenia.<sup>1</sup> The findings could offer a way to target the neuregulin pathway, which has been associated with schizophrenia for more than a decade but has eluded drug discovery efforts because of a lack of validated targets.

Neuregulin 1 (NRG1) and its receptor, epidermal growth factor receptor 4 (EGFR4; HER4; ErbB4), are expressed in regions of the developing brain. The molecules mediate the proliferation of neuronal progenitor cells and drive neuronal migration, axon outgrowth and synapse formation.<sup>2</sup>

Over the past decade, several labs have independently identified genetic mutations in the *NRG1* and *ErbB4* genes of patients with schizophrenia, suggesting that signaling through the NRG1-ErbB4 pathway may be altered in the disease.<sup>3-6</sup> Moreover, *Nrg1* and *ErbB4* mutant mice show behavioral alterations that are similar to the behavior of some standard schizophrenia mouse models.<sup>7,8</sup>

Although those findings suggested targeting NRG1-ErbB4 signaling could help treat some forms of schizophrenia, researchers avoided going after NRG1 or ErbB4 directly because those proteins play an essential role in a variety of CNS cell types.

The NIH team, led by Amanda Law and Daniel Weinberger, decided to look for targets downstream of NRG1 and ErbB4. In particular, they noted that the ErbB4 isoform CYT-1 had a binding site for phosphoinositide 3-kinase (PI3K). That finding suggested that PI3K signaling might also be dysregulated in cells expressing mutant forms of ErbB4 and that PI3K inhibitors could be used to target NRG1-ErbB4 signaling downstream.

Law is a senior research fellow in the Clinical Brain Disorders Branch of the NIH's **National Institute of Mental Health**. Weinberger is a senior investigator in the same department.

The researchers first studied lymphoblastoid B cell lines (LCLs) to determine whether genetic mutations in *ErbB4* indeed correlated with alterations in PI3K signaling. Peripheral LCLs from patients with schizophrenia express some of the same *ErbB4* mutants that occur in the brain and are useful systems for studying dysregulated NRG1-ErbB4 signaling.

In LCLs from patients with schizophrenia, mRNA levels of the catalytic subunit of the PI3K $\delta$  isoform were significantly greater than those in LCLs from healthy controls ( $p=0.002$ ). The higher PI3K $\delta$



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mRNA levels were significantly correlated with an ErbB4 mutant that is associated with risk for schizophrenia ( $p=0.01$ ).

Based on those findings, the researchers hypothesized that lowering PI3K $\delta$  activity could help restore NRG1-ErbB4 signaling and treat schizophrenia.

The team treated two rodent models of schizophrenia with IC87114, a small molecule research compound that is highly selective for the PI3K $\delta$  isoform.

In a mouse model of amphetamine-induced psychosis, intraperitoneal delivery of IC87114 significantly decreased psychotic hyperlocomotion compared with vehicle delivery ( $p<0.05$ ). In a rat model of neurodevelopmental schizophrenia, IC87114 reversed sensorimotor deficits, whereas vehicle had no effect ( $p<0.009$ ).

Finally, genetic analysis of two schizophrenic families revealed SNPs in the promoter and intronic regions of the PI3K $\delta$  gene. That analysis suggested that disruptions in the neuregulin signaling pathway may be caused not only by mutations in the NRG1 and ErbB4 genes but also by mutations in genes encoding downstream effectors such as PI3K $\delta$ .

The findings were published in the *Proceedings of the National Academy of Sciences*.

**Many more steps**

The researchers now need to see whether the changes in PI3K $\delta$  activity they observed in human LCLs are replicated in a more disease-relevant tissue such as human postmortem brain samples, said Chang-Gyu Hahn. PI3K $\delta$  inhibition could also be directly tested in those samples, he said.

Hahn is associate professor of psychiatry at the **Perelman School of Medicine at the University of Pennsylvania**. In 2006, Hahn and colleagues published in *Nature Medicine* that NRG1-ErbB4 signaling suppressed activation of NMDAR in schizophrenia.<sup>9</sup>

Hahn said more mechanistic work in mice should improve understanding of how altered PI3K activity contributes to the schizophrenia phenotype. “Genetic

variation in a single gene, whether it be ErbB4 or PI3K $\delta$ , is not the underlying cause of schizophrenia. Rather, the disease is caused by variation in many genes encoding proteins involved in multiple pathways. Thus, they need to map out and understand how the NRG1-ErbB4-PI3K pathway interacts with proteins in other pathways to give rise to the complex schizophrenia phenotype,” he said.

Such work “could not only identify other druggable proteins PI3K $\delta$  interacts with, such as AKT or GSK3B, but also suggest additional ways of blocking the effects of PI3K $\delta$  signaling in schizophrenia,” Hahn told SciBX.

Corresponding author Law said her team is now “investigating the role of PI3K $\delta$  in brain development and function using approaches in humans and rodents.”

**“Genetic variation in a single gene, whether it be ErbB4 or PI3K $\delta$ , is not the underlying cause of schizophrenia. Rather, the disease is caused by variation in many genes encoding proteins involved in multiple pathways.”**

**—Chang-Gyu Hahn,  
Perelman School of Medicine at  
the University of Pennsylvania**

She added that the group also is “examining how modulation of the protein either pharmacologically or genetically impacts neuronal development, brain maturation and behaviors related to schizophrenia.”

Law and colleagues are also determining which PI3K $\delta$ -selective inhibitors would be most suitable for additional preclinical studies and trials in schizophrenia. She declined to provide additional details.

The lead PI3K $\delta$ -selective inhibitor in clinical development is GS 1101 (CAL-101) from **Gilead Sciences Inc.** The compound is in Phase III testing to treat relapsed chronic lymphocytic leukemia (CLL). GS 1101 resulted from the chemical and pharmacological optimization of IC87114, the research compound used in the paper.

Gilead did not respond to requests for comment.

The *PNAS* findings are patented and available for licensing from the NIH.

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#### COMPANIES AND INSTITUTIONS MENTIONED

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# OutFOXing tumors

By Tracey Baas, Senior Editor

A Mount Sinai School of Medicine and Case Western Reserve University team has found a new use for the dopamine receptor antagonist trifluoperazine: restoring the sensitivity of tumors to epidermal growth factor receptor inhibitors.<sup>1</sup> The key is trifluoperazine's off-target activity related to the export of the tumor suppressor forkhead box O1, which suggests other drugs in the class also could be repurposed to treat resistant cancers.

Although epidermal growth factor receptor (EGFR) inhibitors are a mainstay for treating lung cancers, the drugs are limited by primary or acquired drug resistance that can arise through multiple molecular mechanisms.<sup>2-4</sup>

To better understand the mediators of that resistance, the Sinai-Case Western group focused on two tumor suppressors: Kruppel-like factor 6 (KLF6; COPEB; ZF9) and forkhead box O1 (FOXO1). Prior studies showed that KLF6 levels are lower in lung adenocarcinomas than in matched normal lung tissue.

FOXO1 is the direct transcriptional activator of KLF6 and is inactivated in cancers. The inactivation occurs when FOXO1 is sequestered in the cytoplasm instead of the nucleus where it normally localizes.<sup>5,6</sup>

In mice with EGFR-activated lung adenocarcinoma, the EGFR inhibitor Tarceva erlotinib induced apoptosis and increased levels of KLF6 compared with those in control animals. Moreover, in human EGFR-activated lung adenocarcinoma cell lines that were sensitive to Tarceva, cells given the drug showed greater levels of KLF6, nuclear accumulation of FOXO1 and apoptosis than untreated cells.

By contrast, human EGFR-activated lung adenocarcinoma cell lines that were Tarceva resistant did not undergo apoptosis, had no KLF6 activation and had FOXO1 that remained in the cytoplasm.

**“Our combination of trifluoperazine and erlotinib resulted in a successful therapeutic strategy because the combination provides a marked synergy due to a known mechanism of action—nuclear accumulation of FOXO1 and increased expression of KLF6.”**

—Goutham Narla,  
Case Western Reserve University

In the Tarceva-sensitive cell lines, small interfering RNA targeting FOXO1 or KLF6 prevented drug-mediated apoptosis, suggesting FOXO1 and KLF6 are necessary for Tarceva-mediated apoptosis and sensitivity to anti-EGFR therapy.

The next step was to try to re-establish sensitivity to Tarceva by enhancing the nuclear accumulation of FOXO1 and the subsequent upregulation of KLF6.

To do so, the researchers turned to trifluoperazine, which is approved as an antipsychotic and antiemetic. The drug had been tried in cancer trials in combination

with chemotherapy because trifluoperazine has off-target activity on the p-glycoprotein drug resistance pump, although none of the studies bore fruit.<sup>7-10</sup>

## Box 1. Honing in on differentiation.

A McMaster University team led by Mick Bhatia has used a human pluripotent stem cell (hPSC) line that reproduces neoplastic properties of somatic cancer stem cells<sup>14</sup> to develop a screening platform to identify compounds able to selectively target neoplastic cells and not normal hPSCs.<sup>15</sup>

Cancer stem cells are characterized by enhanced self-renewal with limited cellular differentiation, which drives tumor growth. However, the lack of a robust *in vitro* assay to interrogate human cancer stem cell differentiation has made it difficult to develop therapeutics that interrupt the process.

Bhatia's team set out to develop such an assay. He is professor of biochemistry and biomedical sciences at McMaster University and director and senior scientist at the McMaster Stem Cell and Cancer Research Institute.

The group used neoplastic hPSCs and normal hPSCs expressing GFP reporters to screen compound libraries. A decrease in the reporters indicated a loss of self-renewal and an induction of differentiation.

Hits from the screen included thioridazine, fluphenazine, prochlorperazine, rapamycin and Teva Pharmaceutical Industries Ltd.'s lestaurotinib.

Thioridazine, fluphenazine and prochlorperazine are dopamine receptor antagonists. Rapamycin is a mammalian target of rapamycin (mTOR; FRAP; RAFT1) inhibitor, and the tyrosine kinase inhibitor lestaurotinib is in Phase I/II testing for myeloproliferative disorder.

The team next set out to validate that thioridazine could block cancer progression *in vivo*. In mice, thioridazine decreased leukemic stem cell engraftment compared with vehicle.

“Using a 2,446-compound library, our screening platform provided us with 26 possible hits, with thioridazine being attractive to us because it exhibited the lowest EC<sub>50</sub> in neoplastic stem cells without affecting normal stem cells and is a known antipsychotic with FDA approval,” said Bhatia. “Although our library didn't contain trifluoperazine itself—Narla's hit—our screen did identify a couple of trifluoperazine analogs as potential anticancer therapeutics.”

He added, “I think our screening platform is very amenable for identifying anticancer therapeutics. Typical assays show if compounds affect cancerous stem cells” but do not show what happens to normal cells. “Our platform can inform you if a compound will affect only neoplastic cells and spare normal cells.”

McMaster University has mature provisional patents for the screening technology, which is licensed to Actium Research Inc.

—TB

In 2003, a team at **Harvard Medical School** and the **Dana-Farber Cancer Institute** showed the molecule also was an effective nuclear export inhibitor of FOXO1.<sup>11</sup>

In Tarceva-resistant human adenocarcinoma cell lines, trifluoperazine increased nuclear accumulation of FOXO1 and levels of KLF6 compared with vehicle. In mice with human-derived Tarceva-resistant tumors, trifluoperazine plus Tarceva increased levels of KLF6 and apoptosis and decreased tumor volume compared with Tarceva alone.

The findings could help explain the biology underlying prior observations that both schizophrenic patients receiving dopamine receptor antagonists and dopaminergic-deficient Parkinson's disease patients have a lower incidence of some cancers than the general population.<sup>12,13</sup>

Results were published in *The Journal of Clinical Investigation*.

Tarceva is marketed by **Astellas Pharma Inc.**, **Chugai Pharmaceutical Co. Ltd.** and **Roche** for non-small cell lung cancer (NSCLC) and pancreatic cancer.

### Eye on the target

According to Goutham Narla, Mount Sinai and Case Western team leader and assistant professor of medicine and transformative molecular medicine at Case Western, "Our combination of trifluoperazine and erlotinib resulted in a successful therapeutic strategy because the combination provides a marked synergy due to a known mechanism of action—nuclear accumulation of FOXO1 and increased expression of KLF6."

Narla thinks it would be a good idea to "go back and screen other FDA-approved drugs of this class to see if they could be resurrected to treat anti-EGFR-resistant cancers."

Because dopamine receptors are a subclass of G protein-coupled receptors (GPCRs), Narla said the repurposing search could be far-reaching.

"Compounds that target dopamine receptors or GPCRs might also affect the nuclear accumulation of FOXO1 or other downstream mediators of EGFR signaling, which would have before been considered off-target activity considering their original purpose," he said.

He added, "Drugs that are just sitting on the shelf because they had shown a suboptimal profile as GPCR antagonists could be rescreened as anticancer therapeutics. We have been using cancer cell viability assays to reevaluate GPCR antagonists as anticancer agents" but want to take a step forward and incorporate a new assay being developed by Mick Bhatia (see Box 1, "Honing in on differentiation").

In addition to looking for repurposing opportunities, the group is synthesizing analogs of trifluoperazine. The molecule's "backbone is a rich scaffold that can be derivatized to provide us a compound with improved pharmacology, particularly with respect to CNS effects," noted

**"Drugs that are just sitting on the shelf because they had shown a suboptimal profile as GPCR antagonists could be rescreened as anticancer therapeutics."**

—Goutham Narla,  
Case Western Reserve University

Narla. "Michael Ohlmeyer will be leading the medicinal chemistry aspect of the project, and his team was a recipient of the 2012 NYCIF BioAccelerate prize for this work." The \$250,000 award for one year is intended to fund biomedical research with commercial promise.

Ohlmeyer is an associate professor of structural and chemical biology at the Mount Sinai School of Medicine. He cofounded

chemistry company Pharmacopeia Inc., now **Accelrys Inc.**, and is an author on the *JCI* paper.

Other next steps include clinical trials and testing the combination of trifluoperazine with other EGFR-targeting therapies in other cancers.

Mount Sinai has filed a patent application covering the work, which is available for licensing.

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**Mount Sinai School of Medicine**, New York, N.Y.  
**Roche** (SIX:ROG; OTCQX:RHHBY), Basel, Switzerland  
**Teva Pharmaceutical Industries Ltd.** (NYSE:TEVA), Petah Tikva, Israel

# Getting AGRP on obesity

By Kai-Jye Lou, Staff Writer

Researchers in New York have identified G protein-coupled receptor 17 as a target on agouti related protein-expressing neurons, which are known to regulate multiple factors related to obesity.<sup>1</sup> The findings open up a new molecular signaling pathway to mine for targets to control obesity—earlier attempts to inhibit these neurons via insulin and leptin signaling pathways have had little success.

Inhibition of hypothalamic neurons that express agouti related protein (AGRP) is known to decrease food intake, promote body leanness and improve glucose homeostasis. Although insulin and leptin inhibit the activity of these neurons via their respective receptors, studies to evaluate the activation of these hormonal signaling pathways have suggested that neither pathway alone exerts full control over AGRP neuron-mediated food intake and glucose homeostasis.<sup>2,3</sup>

Moreover, resistance to insulin and leptin develops in response to diet-induced obesity.<sup>4</sup>

**Figure 1. Model for processes mediated by FOXO1 in AGRP neurons.** Researchers have now elucidated the role of forkhead box O1 (FOXO1) transcription factor signaling in hypothalamic neurons that express agouti related protein (AGRP). In the process, the researchers identified G protein-coupled receptor 17 (GPR17) as a potential therapeutic target to help control obesity.

(I) In AGRP neurons with functional FOXO1, activation of GPR17 increases food intake [a]. This is thought to occur via modulation of downstream ion channels [b] in a manner that stimulates the release of neuropeptide Y (NPY) and AGRP [c]. The peptide and protein are both known to increase food intake.

Antagonizing GPR17 has the opposite effects.

(II) Knocking out *FOXO1* in AGRP neurons decreases the expression of GPR17 [a] and leads to less food intake than normal *FOXO1* expression. Loss of the transcription factor also improves glucose homeostasis, increases sensitivity to insulin and leptin [b] and leads to greater lean body mass.

At this time, it is not known whether GPR17 antagonism itself will increase glucose homeostasis, body leanness and sensitivity to leptin and insulin. (Figure based on Figure 7G in ref. 1.)

Thus, a group led by Domenico Accili, professor of medicine and director of the **Columbia University** Diabetes and Endocrinology Research Center, looked into alternative pathways that could be targeted to inhibit the activity of AGRP neurons.

The group first looked upstream at the forkhead box O1 (FOXO1) transcription factor because it regulates both leptin and insulin signaling (see Figure 1, “Model for processes mediated by FOXO1 in AGRP neurons”).<sup>5,6</sup> In mice, knockout of *Foxo1* in hypothalamic *Agrp* neurons decreased food intake and body fat mass and increased body lean mass,

glucose homeostasis and sensitivity to both leptin and insulin compared with wild-type *Foxo1* expression.

However, FOXO1 is a transcription factor and not readily druggable. Thus, Accili’s team used transcriptional profiling to identify downstream targets of Foxo1 in the mouse *Agrp* neurons.

“After observing the beneficial effects in the *Foxo1*-deficient mice, we wanted to know whether there is a FOXO1-regulated pathway that would allow us to skirt around direct targeting of the insulin and leptin receptors”

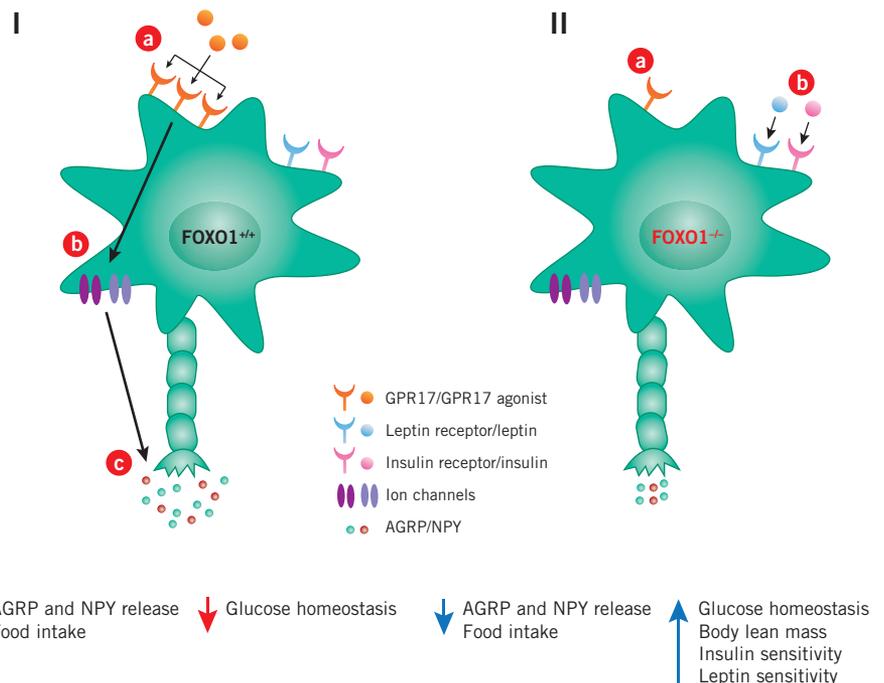
and the transcription factor, said Accili.

Transcriptional profiling studies revealed that *Foxo1*-deficient mouse *Agrp* neurons had about 10-fold lower *G protein-coupled receptor 17* (*GPR17*) mRNA levels than nondeficient *Agrp* neurons.

In wild-type mice, intraventricular injection of the GPR17 antagonist

“After observing the beneficial effects in the *Foxo1*-deficient mice, we wanted to know whether there is a FOXO1-regulated pathway that would allow us to skirt around direct targeting of the insulin and leptin receptors.”

—Domenico Accili,  
Columbia University



cangrelor significantly decreased food intake compared with saline injection, whereas an agonist of the receptor increased food intake. These differences were not seen in mice with *Foxo1* knocked out in *Agrp* neurons.

Cangrelor is a reversible antagonist of purinergic receptor P2Y G protein-coupled 12 (P2RY12; P2Y12). GPR17 has been described as a P2Y-like receptor.<sup>7</sup>

**The Medicines Co.** and **AstraZeneca plc** have cangrelor in Phase III testing to prevent platelet activation and aggregation in patients undergoing percutaneous coronary intervention.

Results were published in *Cell*. The team included researchers from the **Albert Einstein College of Medicine of Yeshiva University** and **Yale School of Medicine**.

“We got interested in GPR17 for two reasons: we saw a 10-fold reduction in *Gpr17* mRNA expression levels in response to knocking out *Foxo1*, and we also knew of chemical compounds that activate and inhibit the receptor,” said Accili.

“The development of resistance has been a key problem with earlier strategies to target AGRP neurons, so G protein-coupled receptors such as GPR17 might provide an alternative route to modulating the endogenous activity of these neurons,” added Jens Brüning, director of the **Max Planck Institute for Neurological Research**.

However, he said it will be important to determine whether AGRP neurons could develop resistance against GPR17-targeting strategies.

Accili acknowledged that desensitization effects can occur with molecules that target GPCRs. However, he said a GPR17 antagonist “would not be something that one would use in the chronic setting, and the effect we are most interested in is its ability to reduce food intake, which will be relevant at the time of a meal.”

Although loss of efficacy from desensitization effects is a concern, it is generally more relevant to the development of long-acting drugs or those that will be used in chronic settings. Most appetite suppressants that promote weight loss are approved for short-term use of up to 12 weeks, though doctors can prescribe the drugs off-label for longer treatment periods.

### A new opportunity

Researchers now want to see a more comprehensive suite of studies characterizing the effects of antagonizing GPR17.

“The team used a modern screening process to understand the role of FOXO1 signaling in these neurons, then worked their way back to GPR17 and showed the effects of modulating the receptor on food intake,” said Randy Seeley, a professor and director of the Cincinnati Diabetes and Obesity Center at the **University of Cincinnati**. “The findings show that understanding this circuit could lead to the identification of new targets and strategies for controlling body weight and also clearly demonstrate the mechanistic role that GPR17 plays in this circuit.”

**“The development of resistance has been a key problem with earlier strategies to target AGRP neurons, so G protein-coupled receptors such as GPR17 might provide an alternative route to modulating the endogenous activity of these neurons.”**

**—Jens Brüning,  
Max Planck Institute for  
Neurological Research**

Brüning noted that in addition to reducing food intake, antagonizing GPR17 on AGRP neurons also could have beneficial effects on glucose metabolism. “Based on our own work and that of others, we have demonstrated that these neurons becoming insulin resistant contributes to the deterioration of peripheral glucose metabolism. Thus, altering their activity via GPR17-dependent signaling could circumvent this deterioration,” he told *SciBX*.

Moreover, Accili said inhibition of GPR17 has been linked to beneficial cardiovascular effects such as reduced blood clotting, improved perfusion of blood into the heart and improved recovery from stroke.

Accili said his group now is trying to develop and characterize the phenotype of a *Gpr17* knockout mouse.

The team has not yet been able to test the effects of GPR17 antagonism on body leanness, glucose homeostasis and sensitivity to leptin and insulin because cangrelor’s short

half-life makes it difficult to design such experiments.

Nevertheless, he said his group plans to carry out studies to evaluate the effects of GPR17 antagonism on these FOXO1-regulated processes in AGRP neurons.

His group also is planning to rerun the mouse GPR17 antagonism studies in large animal models such as nonhuman primates.

Columbia has a pending patent covering GPR17-based approaches to treat obesity and diabetes. The work is available for licensing from **Columbia Technology Ventures**, the university’s technology transfer arm.

Lou, K.-J. *SciBX* 5(28); doi:10.1038/scibx.2012.720  
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### COMPANIES AND INSTITUTIONS MENTIONED

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# SEAing change in R&D

By Kai-Jye Lou, Staff Writer

Researchers at the **University of California, San Francisco, SeaChange Pharmaceuticals Inc.** and the **Novartis Institutes for BioMedical Research** have developed a computational approach for large-scale, automated prediction of binding interactions between molecules and targets that have been associated with adverse drug reactions.<sup>1</sup> The method could help companies improve R&D productivity by pointing to safety signals and helping prioritize candidates *in silico*.

The computational approach uses a statistics-based chemoinformatics technique called the similarity ensemble approach (SEA), which the UCSF group first described in 2007.<sup>2</sup> SEA predicts whether a molecule will bind a target based on the similarity of the compound's chemical groups to known ligands of the target.

In March 2009, the UCSF group spun out SeaChange to develop and commercialize SEA-based computational methods that could help improve and speed up early drug R&D.<sup>3</sup> That year, the group also showed that a SEA-based computational method could predict new molecular targets for 878 FDA-approved small molecule drugs and another 2,787 small molecule reagents.<sup>4</sup>

Despite predicting a broad swath of new off-target interactions for existing drugs, the researchers still needed to manually run a laborious series of experimental assays to confirm whether an interaction actually occurred and to predict case by case whether such an interaction could lead to adverse effects.

A pivotal contribution came in 2010, when NIBR offered to test the UCSF-SeaChange predictions of drug-target interactions on a large scale, with the goal of linking them to adverse effects. The institute also brought in its own experimental and computational expertise.

NIBR is the global pharmaceutical research organization for **Novartis AG**.

"After our 2009 paper, the molecular toxicology group at NIBR got interested in our work and presented us with the opportunity to test the approach at scale," said Brian Shoichet, a professor in the Department of Pharmaceutical Chemistry at UCSF and a cofounder and scientific advisor to SeaChange.

"Novartis has access to a large number of proprietary databases that are unavailable to the public and also had the resources to test the blind predictions generated with our computational methods via a truly impressive number of high-quality experimental assays," added SeaChange cofounder and COO Michael Keiser. "With these results and databases in hand, they made it possible to calculate which predictions may be most relevant to any given drug's actual side effects in patients."

The partners used SEA to generate a list of 1,644 predicted binding interactions between 656 marketed drugs and 73 proteins that have established associations with adverse drug reactions. Next, they used

information contained in the publicly accessible ChEMBL database to confirm the validity of 403 of the predicted interactions.

For 1,042 of the 1,241 interactions that could not be confirmed with ChEMBL, the group turned to the proprietary databases available to Novartis and experimental assays. Based on this, 48% of the interactions were confirmed, 46% were disproven and 6% remained ambiguous.

Keiser said these preliminary performance metrics of the SEA-based method are an order of magnitude better than those of traditional *in silico* approaches for drug discovery.

"Unsupervised computational approaches, such as those that use the 3D structure of a protein to identify molecules with shapes that could bind to a target site, typically have hit rates in the low single-digit percentages or below" in terms of confirming the predictions, he told *SciBX*. "I was astounded by our hit rate of 48%."

In the second half of the study, the team at NIBR linked the newly confirmed drug-target interactions with patient data on adverse drug reactions for known drugs. The NIBR researchers then used these associations to create a series of networks that linked drugs to predicted targets and adverse drug reactions.

As an example, one of the networks generated from the combined datasets suggested chlorotrianisene's known side effect of upper abdominal pain could be due to a previously unrecognized inhibition of cyclooxygenase-1 (COX-1).

Chlorotrianisene is a generic synthetic estrogen that is marketed to treat symptoms of menopause, deficiencies in ovary function and prostate cancer.

Results were published in *Nature*. Shoichet is a co-corresponding author on the paper, and Keiser is the colead author. The other colead author is Eugen Lounkine, an investigator at NIBR.

"Using this and future improved versions

of the method can be a game changer in

how we could use *in silico* predictions for off-target effects," said Laszlo Urban, global head of preclinical safety profiling at NIBR and a co-corresponding author on the paper. "This approach can be used during early drug discovery to identify unexpected off targets associated with potentially dangerous or limiting side effects, initiate *in vitro*-*in vivo* testing and, if necessary, risk mitigation processes" such as modifying a molecule's structure to eliminate potentially unsafe drug-target interactions or removing such molecules from development altogether.

He added, "Another possible use is for exploiting unintended off-target/on-target pairings that might offer improved therapeutic opportunities. Thus the system also could be used to reposition marketed drugs."

## Prioritizing early

Lead generation and lead optimization to get to a clinical candidate typically require around 3.5 years and \$12.5 million.<sup>5</sup> The SEA-based computational method could improve the *in silico* candidate selection process and reduce the burden of more resource-intensive *in vitro* and *in vivo* assays.

The algorithmic methods underlying the SEA-based computational

**"Using this and future improved versions of the method can be a game changer in how we could use *in silico* predictions for off-target effects."**

—Laszlo Urban,  
Novartis Institutes for BioMedical  
Research

approach are unpatented. Third parties are free to develop their own computational software packages using SEA-based methods for their own applications. SeaChange charges a fee to its clients for such services.

“The major impact is expected when the method is applied to the design of drug candidates because they can be tested prior to synthesis, and it also can pinpoint off-target effects,” said Urban. “Regulatory *in vivo* pharmacology studies largely remain unaffected but could become more focused.”

“Our approach could help companies increase the productivity of their medicinal chemistry programs by improving the way they prioritize molecules early in the drug R&D process and by helping them choose which safety studies to focus on first,” added Keiser.

He noted that the bulk of the costs associated with use of SEA-based computational methods are in setting up a system and optimizing it for a company’s chemistry and biological target space.

The costs of running *in silico* screens with a SEA-based approach after the system is set up will primarily come from maintaining and organizing high-quality discovery data for the methods to use, he added.

The partners are now trying to improve the performance of the SEA-based computational strategy and are evaluating it in additional drug R&D settings.

Urban said Novartis is trying to further improve the predictive performance of the computational approach by using larger sets of data. The pharma is using its own implementation of computational methods related to the SEA methodology.

Keiser said SeaChange is applying SEA-based computational methods to identify new potential indications for existing drugs.

**“The major impact is expected when the method is applied to the design of drug candidates because they can be tested prior to synthesis, and it also can pinpoint off-target effects.”**

**—Laszlo Urban,  
Novartis Institutes for BioMedical  
Research**

He said SeaChange and UCSF also are refining the methods to improve predictive performance. Finally, he said the university and company are developing SEA-based methods for use in more specific drug R&D settings, such as augmenting standard preclinical safety panels by predicting a compound’s interactions with a wide range of adverse drug reaction targets.

SeaChange’s software packages using SEA-based computational methods are protected by trademark and copyright, and custom

implementations of it are available for licensing discussions.

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## This week in therapeutics

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

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

| Indication  | Target/marker/pathway  | Summary   | Licensing status                               | Publication and contact information  |
|---|--|---|--|--|
| <b>Autoimmune disease</b>   |  |   |  |  |
| Osteoarthritis  | Guanine nucleotide binding protein-like 3 (GNL3; nucleostemin) | Genomewide association studies identified mutations in the <i>GNL3</i> gene that could help predict susceptibility to osteoarthritis. A study comparing 7,410 European patients with osteoarthritis to European controls identified 5 missense mutations in the <i>GNL3</i> gene that conferred increased risk for the disease. Those findings were validated in a second cohort of 7,473 patients and 42,938 controls. In chondrocytes from patients with osteoarthritis, <i>GNL3</i> -encoded nucleostemin protein levels were higher than those in chondrocytes from healthy controls. Next steps include determining the effect of the susceptibility alleles on protein function.  | Findings unpatented; unavailable for licensing | arcOGEN Consortium and arcOGEN Collaborators. <i>Lancet</i> ; published online July 2, 2012; doi:10.1016/S0140-6736(12)60681-3<br><b>Contact:</b> John Loughlin, Newcastle University, Newcastle upon Tyne, U.K.<br>e-mail: <a href="mailto:john.loughlin@ncl.ac.uk">john.loughlin@ncl.ac.uk</a><br><b>Contact:</b> Eleftheria Zeggini, Wellcome Trust Sanger Institute, Hinxton, U.K.<br>e-mail: <a href="mailto:eleftheria@sanger.ac.uk">eleftheria@sanger.ac.uk</a> |
| <b>SciBX 5(28); doi:10.1038/scibx.2012.722<br/>Published online July 19, 2012</b> |  |   |  |  |
| <b>Cancer</b>   |  |   |  |  |
| Breast cancer; colorectal cancer  | Death effector domain containing (DEDD)                        | Mouse and patient studies suggest enhancing DEDD signaling could help treat and prevent cancer metastasis. In tumor tissues from 60 patients with breast cancer and 60 patients with colorectal cancer, high DEDD levels were correlated with increased survival. In a mouse xenograft model of human breast cancer, small hairpin RNA against <i>DEDD</i> increased tumor growth and metastasis compared with control shRNA. Next steps could include screening for compounds that enhance DEDD signaling.   | Patent and licensing status unavailable        | Lv, Q. <i>et al. Cancer Res.</i> ; published online June 19, 2012; doi:10.1158/0008-5472.CAN-11-3832<br><b>Contact:</b> Zhuo-Wei Hu, Chinese Academy of Medical Sciences and Peking Union Medical College, Beijing, China<br>e-mail: <a href="mailto:huzhuowei@imm.ac.cn">huzhuowei@imm.ac.cn</a>  |
| <b>SciBX 5(28); doi:10.1038/scibx.2012.723<br/>Published online July 19, 2012</b> |  |   |  |  |
| Mantle cell lymphoma (MCL)  | Signal transducer and activator of transcription 3 (STAT3)     | <i>In vitro</i> and mouse studies suggest inhibiting STAT3 could enhance antitumor immunity to help treat MCL. In cultured mouse B cell lymphoma cells, expression of a dominant-negative <i>Stat3</i> mutant to inhibit the protein's signaling increased antigen-specific T cell activation compared with that seen in mock-transfected controls. In mice injected with mouse MCL or B cell lymphoma cells, a <i>Stat3</i> inhibitor decreased tumor growth compared with vehicle. Immunodeficient mice given the <i>Stat3</i> inhibitor did not have an antitumor response. Next steps could include conducting clinical trials of <i>STAT3</i> inhibitors in patients with MCL and testing the effects of <i>STAT3</i> inhibition in preclinical models of other B cell malignancies.<br>At least four companies have <i>STAT3</i> inhibitors in clinical and preclinical testing to treat various cancers. | Patent and licensing status unavailable        | Cheng, F. <i>et al. Cancer Res.</i> ; published online June 22, 2012; doi:10.1158/0008-5472.CAN-11-3619<br><b>Contact:</b> Eduardo M. Sotomayor, H. Lee Moffitt Cancer Center & Research Institute, Tampa, Fla.<br>e-mail: <a href="mailto:eduardo.sotomayor@moffitt.org">eduardo.sotomayor@moffitt.org</a>  |
| <b>SciBX 5(28); doi:10.1038/scibx.2012.724<br/>Published online July 19, 2012</b> |  |   |  |  |

## This week in therapeutics (continued)

| Indication  | Target/marker/<br>pathway               | Summary  | Licensing status  | Publication and contact<br>information  |
|---|---|--|---|---|
| Non-small cell lung cancer (NSCLC)                        | AXL receptor tyrosine kinase (AXL; UFO) | <i>In vitro</i> , patient sample and mouse studies suggest inhibiting AXL could help treat epidermal growth factor receptor (EGFR) inhibitor-resistant NSCLC. In a human NSCLC cell line with acquired resistance to the EGFR inhibitor Tarceva erlotinib, AXL expression was greater than that in Tarceva-sensitive cells. In tumor samples from patients with acquired resistance to Tarceva, AXL expression was greater than that in the patient samples prior to treatment. In mice with human Tarceva-resistant AXL-overexpressing NSCLC xenografts, AXL-targeting small hairpin RNA or pharmacological AXL inhibition restored sensitivity to Tarceva. Next steps include identifying potent and selective AXL inhibitors.<br>BerGenBio A/S has the AXL inhibitor BGB324 in preclinical testing to treat cancer.<br>Astellas Pharma Inc., Roche and Chugai Pharmaceutical Co. Ltd. market Tarceva to treat NSCLC and pancreatic cancer.<br><br><b>SciBX 5(28); doi:10.1038/scibx.2012.725</b><br><b>Published online July 19, 2012</b> | Findings unpatented; unavailable for licensing  | Zhang, Z. <i>et al. Nat. Genet.</i> ; published online July 1, 2012; doi:10.1038/ng.2330<br><b>Contact:</b> Trever G. Bivona, University of California, San Francisco, Calif.<br>e-mail:<br><a href="mailto:tbivona@medicine.ucsf.edu">tbivona@medicine.ucsf.edu</a>  |
| Non-small cell lung cancer (NSCLC)                        | <i>BRAF</i>                             | Patient and cell culture studies suggest NSCLC patients with inactivating <i>BRAF</i> mutations may respond to Sprycel dasatinib. In a previously conducted Phase II trial of Sprycel in 34 patients with NSCLC, one patient went into complete remission, whereas none of the other patients responded. Genomic analysis of tumor tissue identified a <i>BRAF</i> -inactivating mutation that was present exclusively in that one patient. In NSCLC cell lines with inactivating <i>BRAF</i> mutations, Sprycel induced senescence that was irreversible after four days of treatment. Next steps include a clinical trial of Sprycel in patients with NSCLC that have an inactivating <i>BRAF</i> mutation.<br>Bristol-Myers Squibb Co. and Otsuka Pharmaceutical Co. Ltd. market Sprycel for acute lymphoblastic leukemia (ALL) and chronic myelogenous leukemia (CML).<br><br><b>SciBX 5(28); doi:10.1038/scibx.2012.726</b><br><b>Published online July 19, 2012</b>  | Patent application filed covering utilization of the <i>BRAF</i> mutant to identify patients; available for licensing | Sen, B. <i>et al. Sci. Transl. Med.</i> ; published online May 30, 2012; doi:10.1126/scitranslmed.3003513<br><b>Contact:</b> Faye M. Johnson, The University of Texas MD Anderson Cancer Center, Houston, Texas<br>e-mail:<br><a href="mailto:fmjohns@mdanderson.org">fmjohns@mdanderson.org</a>              |
| Squamous cell carcinoma (SCC); basal cell carcinoma (BCC) | Jun (AP1) proto-oncogene                | Mouse studies identified a Jun mRNA-targeting DNzyme that could help treat SCC and BCC. DNzymes are single-stranded DNA molecules that bind to and cleave RNA molecules. In mouse models of SCC and BCC, intratumoral delivery of a Jun mRNA-targeting DNzyme blocked tumor angiogenesis and decreased tumor growth compared with delivery of vehicle. Next steps could include optimizing the identified DNzyme for topical delivery.<br><br><b>SciBX 5(28); doi:10.1038/scibx.2012.727</b><br><b>Published online July 19, 2012</b>  | Patent and licensing status unavailable   | Cai, H. <i>et al. Sci. Transl. Med.</i> ; published online June 20, 2012; doi:10.1126/scitranslmed.3003960<br><b>Contact:</b> Levon M. Khachigian, The University of New South Wales, Sydney, New South Wales, Australia<br>e-mail:<br><a href="mailto:l.khachigian@unsw.edu.au">l.khachigian@unsw.edu.au</a> |

## This week in therapeutics (continued)

| Indication                      | Target/marker/<br>pathway  | Summary  | Licensing status                                  | Publication and contact<br>information  |
|---------------------------------|--|--|---|---|
| <b>Gastrointestinal disease</b> |  |  |   |   |
| Colitis                         | Epidermal growth factor receptor (EGFR)  | Mouse and infant studies suggest amniotic fluid could be used to prevent necrotizing enterocolitis (NEC). In a mouse model of NEC, newborn mice receiving daily enteral delivery of amniotic fluid had less severe NEC than mice given Egf-depleted amniotic fluid or no treatment. In humans, premature infants with NEC had lower expression of intestinal EGFR than premature infants with resolved NEC. Next steps include clinical trials of the amniotic fluid delivery strategy to prevent NEC in premature infants.<br><br><b>SciBX 5(28); doi:10.1038/scibx.2012.728</b><br><b>Published online July 19, 2012</b>   | Patent application filed; available for licensing | Good, M. <i>et al. Proc. Natl. Acad. Sci. USA</i> ; published online June 25, 2012; doi:10.1073/pnas.1200856109<br><b>Contact:</b> David J. Hackam, Children's Hospital of Pittsburgh of UPMC, Pittsburgh, Pa.<br>e-mail:<br><a href="mailto:david.hackam@chp.edu">david.hackam@chp.edu</a>   |
| <b>Hematology</b>               |  |  |   |   |
| Immunodeficiency                | CD3e molecule-ε CD3-TCR complex (CD3E)   | Mouse studies suggest anti-CD3E mAbs could help treat Omenn syndrome, a form of severe combined immunodeficiency that is associated with mutations in recombination activating genes (RAGs). In newborn mice with a <i>Rag2</i> mutation, injection of an anti-CD3E mAb increased both the maturation and the expansion of immune-activating thymic cells compared with injection of saline. Next steps include evaluating whether mice pretreated with an anti-CD3E mAb prior to a bone marrow transplant show faster immune system reconstitution than untreated mice.<br><br><b>SciBX 5(28); doi:10.1038/scibx.2012.729</b><br><b>Published online July 19, 2012</b>  | Patented; licensing status undisclosed            | Marrella, V. <i>et al. Blood</i> ; published online June 21, 2012; doi:10.1182/blood-2012-01-406827<br><b>Contact:</b> Anna Villa, The National Research Council, Milan, Italy<br>e-mail:<br><a href="mailto:anna.villa@humanitasresearch.it">anna.villa@humanitasresearch.it</a>   |
| <b>Infectious disease</b>       |  |  |   |   |
| Malaria                         | <i>Plasmodium falciparum</i> lysyl-tRNA synthetase (Pfkrs1)                                      | <i>In vitro</i> and cell culture studies suggest inhibiting Pfkrs1 could help treat liver- and blood-stage malarial infections. A high throughput screen of a natural product library identified cladosporin as a mid-nanomolar inhibitor of blood- and liver-stage <i>P. falciparum</i> proliferation. Emerging cladosporin-resistant <i>P. falciparum</i> showed amplification of the <i>krs1</i> locus, suggesting the gene is the direct target of cladosporin. In an <i>in vitro</i> assay, cladosporin inhibited Pfkrs1 with an IC <sub>50</sub> value of about 60 nM, whereas it had high micromolar concentrations for the human homolog. Next steps could include screening for more drug-like Pfkrs1 inhibitors and testing them in animal models of malaria.<br><br><b>SciBX 5(28); doi:10.1038/scibx.2012.730</b><br><b>Published online July 19, 2012</b> | Patent and licensing status unavailable           | Hoepfner, D. <i>et al. Cell Host Microbe</i> ; published online June 14, 2012; doi:10.1016/j.chom.2012.04.015<br><b>Contact:</b> Dominic Hoepfner, Novartis AG, Basel, Switzerland<br>e-mail:<br><a href="mailto:dominic.hoepfner@novartis.com">dominic.hoepfner@novartis.com</a><br><b>Contact:</b> Elizabeth A. Winzeler, University of California, San Diego, La Jolla, Calif.<br>e-mail:<br><a href="mailto:ewinzeler@ucsd.edu">ewinzeler@ucsd.edu</a>                              |
| <b>Musculoskeletal disease</b>  |  |  |   |   |
| Osteoporosis                    | Bone morphogenetic protein 2 (BMP2); BMP4; bone morphogenetic protein receptor type IA (BMPRI A) | <i>In vitro</i> and mouse studies suggest a BMPRI A-Fc fusion protein could help treat bone-related disorders such as osteoporosis. The fusion protein consisted of mouse Bmpr1a fused to mouse IgG2a-Fc. <i>In vitro</i> , the mBmpr1a-mFc fusion protein bound Bmp2 and Bmp4 with high affinity and prevented downstream signaling. In mice with osteoporosis, animals receiving mBMPRI A-mFc had bone mineral densities similar to those in healthy mice and had greater bone strength than mice given vehicle. Acceleron Pharma Inc. plans to file an IND for the program in 2013. Specific indications have not been disclosed.<br><br><b>SciBX 5(28); doi:10.1038/scibx.2012.731</b><br><b>Published online July 19, 2012</b>  | Patented; licensed to Acceleron Pharma            | Baud'huin, M. <i>et al. Proc. Natl. Acad. Sci. USA</i> ; published online July 3, 2012; doi:10.1073/pnas.1204929109<br><b>Contact:</b> Peter I. Croucher, The University of Sheffield Medical School, Sheffield, U.K.<br>e-mail:<br><a href="mailto:p.croucher@garvan.org.au">p.croucher@garvan.org.au</a><br><b>Contact:</b> R. Scott Pearsall, Acceleron Pharma Inc., Cambridge, Mass.<br>e-mail:<br><a href="mailto:spearsall@acceleronpharma.com">spearsall@acceleronpharma.com</a> |

## This week in therapeutics (continued)

| Indication  | Target/marker/<br>pathway               | Summary   | Licensing status   | Publication and contact<br>information  |
|---|---|---|--|---|
| <b>Neurology</b>                                    |   |   |  |   |
| Alzheimer's disease (AD); Huntington's disease (HD) | Caspase-6 (CASP6; MCH2)                 | <i>In vitro</i> and cell culture studies identified a peptide-based inhibitor of CASP6, which is associated with neurodegenerative diseases such as AD and HD. A screen of a phage display library identified a peptide that bound to the tetramer interface of an inactive form of CASP6, which is called a zymogen. In a neuronal cell line, the peptide blocked the cleavage of a CASP6 substrate. Next steps include screening for small molecules or peptide fragments that target this site and for peptide inhibitors of other caspase zymogens.<br><br><b>SciBX 5(28); doi:10.1038/scibx.2012.732</b><br><b>Published online July 19, 2012</b>  | Patent and licensing status undisclosed  | Stanger, K. <i>et al. Nat. Chem. Biol.</i> ; published online June 10, 2012; doi:10.1038/nchembio.967<br><b>Contact:</b> Rami N. Hannoush, Genentech Inc., South San Francisco, Calif.<br>e-mail: <a href="mailto:hannoush.rami@gene.com">hannoush.rami@gene.com</a>  |
| Depression  | Neuritin (NRN)                          | Rat studies suggest increasing NRN levels could help treat depression. In rat models of chronic unpredictable stress, hippocampal delivery of an Nrn-expressing viral vector led to decreased depressive behaviors compared with delivery of a control viral vector. In rats, small hairpin RNA-mediated knockdown of Nrn led to depression-like behaviors. Next steps could include determining how NRN elicits its antidepressant effects.<br><br><b>SciBX 5(28); doi:10.1038/scibx.2012.733</b><br><b>Published online July 19, 2012</b>   | Patent and licensing status unavailable  | Son, H. <i>et al. Proc. Natl. Acad. Sci. USA</i> ; published online June 25, 2012; doi:10.1073/pnas.1201191109<br><b>Contact:</b> Hyeon Son, Hanyang University, Seoul, South Korea<br>e-mail: <a href="mailto:hyeonsoon@hanyang.ac.kr">hyeonsoon@hanyang.ac.kr</a><br><b>Contact:</b> Ronald S. Duman, Yale University, New Haven, Conn.<br>e-mail: <a href="mailto:ronald.duman@yale.edu">ronald.duman@yale.edu</a> |
| Diabetic neuropathy; pain                           | Epoxide hydrolase                       | Rat studies suggest inhibitors of soluble epoxide hydrolase could help treat pain associated with diabetic neuropathy. In rat models of type 1 diabetes-induced neuropathic pain, three different soluble epoxide hydrolase inhibitors decreased pain-related behaviors compared with vehicle control. Studies of soluble epoxide hydrolase inhibitors in nonrodent models of neuropathic pain and development of more potent analogs are ongoing.<br><br><b>SciBX 5(28); doi:10.1038/scibx.2012.734</b><br><b>Published online July 19, 2012</b>   | Soluble epoxide hydrolase inhibitors patented; available for licensing from the University of California, Davis<br><b>Contact:</b> Barbara Boczar, University of California, Davis, Calif.<br>e-mail: <a href="mailto:baboczar@ucdavis.edu">baboczar@ucdavis.edu</a> | Inceoglu, B. <i>et al. Proc. Natl. Acad. Sci. USA</i> ; published online June 25, 2012; doi:10.1073/pnas.1208708109<br><b>Contact:</b> Bruce D. Hammock, University of California, Davis, Calif.<br>e-mail: <a href="mailto:bdhammock@ucdavis.edu">bdhammock@ucdavis.edu</a>  |
| Neurology; stroke                                   | Protein kinase B (PKB; PKBA; AKT; AKT1) | <i>In vitro</i> and mouse studies identified an AKT activator that could help treat neurological conditions including stroke. A cell-based, high throughput, chemical, genetic screen identified a small molecule AKT activator. In cultured cortical neurons, the AKT activator decreased excitotoxicity-induced neuronal cell death compared with vehicle. In a mouse model of ischemic stroke, intraperitoneal injection of the AKT activator decreased neuronal cell death and lesion size compared with vehicle. Next steps could include testing the activator in additional disease models.<br><br><b>SciBX 5(28); doi:10.1038/scibx.2012.735</b><br><b>Published online July 19, 2012</b> | Patent and licensing status unavailable  | Jo, H. <i>et al. Proc. Natl. Acad. Sci. USA</i> ; published online June 11, 2012; doi:10.1073/pnas.1202810109<br><b>Contact:</b> Hongbo R. Luo, Harvard Medical School and Dana-Farber/Harvard Cancer Center, Boston, Mass.<br>e-mail: <a href="mailto:hongbo.luo@childrens.harvard.edu">hongbo.luo@childrens.harvard.edu</a>   |
| Pain  | $\mu$ -Opioid receptor (OPRM1; MOR)     | Mouse studies identified MOR-activating endomorphin-1 analogs that could help treat pain. In a mouse model of pain, four analogs containing $\alpha$ -methylene- $\beta$ -amino propanoic acid had more potent antinociceptive effects than endomorphin-1. Next steps include optimizing the structure of the lead compound to improve its ability to cross the blood brain barrier.<br><br><b>SciBX 5(28); doi:10.1038/scibx.2012.736</b><br><b>Published online July 19, 2012</b>   | Patent pending in China; unavailable for licensing   | Wang, Y. <i>et al. J. Med. Chem.</i> ; published online June 22, 2012; doi:10.1021/jm300664y<br><b>Contact:</b> Rui Wang, Lanzhou University, Lanzhou, China<br>e-mail: <a href="mailto:wangrui@lzu.edu.cn">wangrui@lzu.edu.cn</a>  |

## This week in therapeutics (continued)

| Indication                                     | Target/marker/<br>pathway                                  | Summary   | Licensing status                               | Publication and contact<br>information   |
|--|--|---|--|--|
| Schizophrenia                                  | Phosphoinositide<br>3-kinase- $\delta$<br>(PI3K $\delta$ ) | <i>In vitro</i> , rat and patient genetic studies suggest inhibitors of PI3K $\delta$ could help treat schizophrenia. In cell lines derived from patients with schizophrenia, PI3K $\delta$ levels were greater than those in cell lines derived from normal controls. In a rat model of schizophrenia, a small molecule inhibitor of PI3K $\delta$ decreased sensory-motor deficits compared with vehicle. In two family-based genetic studies, SNPs in the promoter and intronic regions of the <i>PI3K<math>\delta</math></i> gene were associated with schizophrenia. Next steps include identifying the PI3K $\delta$ inhibitors best suited for targeting the kinase in the brain.<br>GS 1101 (CAL-101), a PI3K $\delta$ -selective inhibitor from Gilead Sciences Inc., is in Phase III testing to treat relapsed chronic lymphocytic leukemia (CLL; <i>see PI3K<math>\delta</math> turns schizophrenic, page 1</i> ). | Patented; available for licensing from the NIH | Law, A.J. <i>et al. Proc. Natl. Acad. Sci. USA</i> ; published online June 11, 2012; doi:10.1073/pnas.1206118109<br><b>Contact:</b> Amanda J. Law, National Institutes of Health, Bethesda, Md.<br>e-mail:<br><a href="mailto:lawa@mail.nih.gov">lawa@mail.nih.gov</a>                         |
| <b>Ophthalmic disease</b>                      |  |   |  |  |
| Diabetic<br>retinopathy;<br>ophthalmic disease | Opticin (OPTC)   | Mouse studies suggest OPTC could decrease neovascularization to help treat retinopathy. In a mouse model of oxygen-induced retinopathy, intravitreal injection of recombinant bovine OPTC decreased neovascularization compared with vehicle injection. Ongoing work includes showing that OPTC can inhibit tumor angiogenesis and growth and identifying antiangiogenic fragments of OPTC.   | Patented; available for licensing              | Le Goff, M.M. <i>et al. J. Biol. Chem.</i> ; published online June 5, 2012; doi:10.1074/jbc.M111.331157<br><b>Contact:</b> Paul N. Bishop, The University of Manchester, Manchester, U.K.<br>e-mail:<br><a href="mailto:paul.bishop@manchester.ac.uk">paul.bishop@manchester.ac.uk</a>         |
| <b>Various</b>                                 |  |   |  |  |
| Atherosclerosis;<br>diabetes; obesity          | Delta-like 4<br>(DLL4)                                     | Mouse studies suggest antagonizing DLL4 could help treat atherosclerosis and metabolic diseases. In a mouse model of diet-induced atherosclerosis, a DLL4-blocking antibody decreased weight gain, severity of atherosclerotic lesions and macrophage numbers in adipose tissue compared with IgG control. In these mice, the DLL4-blocking antibody also increased insulin sensitivity compared with IgG control. Next steps could include testing the effects of chronic DLL4 blockade.<br>OncoMed Pharmaceuticals Inc.'s demcizumab, a human mAb against DLL4, is in Phase I testing for various cancers.<br>Regeneron Pharmaceuticals Inc. and Sanofi have REGN421, a human mAb against DLL4, in Phase I testing for solid tumors.  | Patent and licensing status unavailable        | Fukuda, D. <i>et al. Proc. Natl. Acad. Sci. USA</i> ; published online June 13, 2012; doi:10.1073/pnas.1116889109<br><b>Contact:</b> Masanori Aikawa, Brigham and Women's Hospital, Boston, Mass.<br>e-mail:<br><a href="mailto:maikawa@rics.bwh.harvard.edu">maikawa@rics.bwh.harvard.edu</a> |

## This week in techniques

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

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

| Approach  | Summary   | Licensing status  | Publication and contact information   |
|---|---|---|---|
| <b>Assays &amp; screens</b>   |   |   |   |
| <i>In vitro</i> blood brain barrier (BBB) with pluripotent stem cells                     | <i>In vitro</i> studies suggest human pluripotent stem cells could be used to screen for BBB-modulating compounds. In cell culture, pluripotent stem cell-derived neural progenitor cells treated with media conditioned by endothelial cells differentiated into endothelial cells. When cocultured with astrocytes, the endothelial cells formed tight junctions and had lower electrical resistance than undifferentiated cell culture controls. In an <i>in vitro</i> assay of drug permeability, the astrocyte-endothelial cell culture had greater expression of BBB-associated markers than undifferentiated controls. Next steps include scaling up the coculture system to test for compounds that modulate the BBB or therapeutics that are resistant to BBB exclusion.<br><br><b>SciBX 5(28); doi:10.1038/scibx.2012.740</b><br>Published online July 19, 2012 | Patent pending; available for licensing                                       | Lippmann, E.S. <i>et al. Nat. Biotechnol.</i> ; published online June 24, 2012; doi:10.1038/nbt.2247<br><b>Contact:</b> Eric V. Shusta, University of Wisconsin-Madison, Madison, Wis.<br>e-mail: <a href="mailto:shusta@engr.wisc.edu">shusta@engr.wisc.edu</a><br><b>Contact:</b> Sean P. Palecek, same affiliation as above<br>e-mail: <a href="mailto:palecek@engr.wisc.edu">palecek@engr.wisc.edu</a>          |
| <b>Computational models</b>   |   |   |   |
| Correction and assembly of single-molecule sequencing reads                               | A computational approach for correcting errors in long-read, single-molecule sequencing could aid in developing applications of the technology for biomedical discovery and guiding treatment. An algorithm that trimmed and corrected individual long-read sequences by first mapping short-read sequences to them and then computing a hybrid consensus sequence improved read accuracy from 80% to more than 99.9%. The method provided long transcripts and assemblies from short reads using sequencing data from both prokaryotic and eukaryotic whole genomes. Ongoing work includes evaluating long reads for the automated filling of sequencing gaps in bacterial genomes and effectively separating mixed sequencing samples.<br><br><b>SciBX 5(28); doi:10.1038/scibx.2012.741</b><br>Published online July 19, 2012  | Source code for the software described in the publication is freely available | Koren, S. <i>et al. Nat. Biotechnol.</i> ; published online July 1, 2012; doi:10.1038/nbt.2280<br><b>Contact:</b> Adam M. Phillippy, National Biodefense Analysis and Countermeasures Center, Frederick, Md.<br>e-mail: <a href="mailto:phillippya@nbacc.net">phillippya@nbacc.net</a><br><b>Contact:</b> Sergey Koren, same affiliation as above<br>e-mail: <a href="mailto:korens@nbacc.net">korens@nbacc.net</a> |
| <b>Disease models</b>   |   |   |   |
| Induced pluripotent stem (iPS) cells derived from patients with Huntington's disease (HD) | <i>In vitro</i> studies suggest iPS cell lines generated from patients with HD could help identify new therapeutics. Neural stem cells (NSCs) generated from 14 iPS cell lines derived from patients with HD had HD-associated CAG repeats in the <i>huntingtin (HTT)</i> gene. The NSCs also captured the physiological features of the disease including greater alterations in the actin cytoskeleton, decreased bioenergetics and increased cell death in response to growth factor withdrawal compared with NSCs generated from healthy control-derived iPS cells. Next steps could include using the cells to look for disease biomarkers and to screen for therapeutic candidates.<br><br><b>SciBX 5(28); doi:10.1038/scibx.2012.742</b><br>Published online July 19, 2012   | Patent and licensing status unavailable                                       | The HD iPSC Consortium. <i>Cell Stem Cell</i> ; published online June 28, 2012; doi:10.1016/j.stem.2012.04.027<br><b>Contact:</b> Clive Svendsen, Cedars-Sinai Medical Center, Los Angeles, Calif.<br>e-mail: <a href="mailto:clive.svendsen@cshs.org">clive.svendsen@cshs.org</a>  |
| Mouse model of acrodermatitis enteropathica   | A mouse model of acrodermatitis enteropathica could help identify therapeutics for the rare lethal metabolic disorder that impairs zinc uptake. More than 32 mutations or variants of <i>solute carrier family 39 zinc transporter member 4 (SLC39A4)</i> have been associated with human acrodermatitis enteropathica. Mice with conditional intestinal enterocyte-specific <i>Slc39a4</i> knockout had features of the human disease including diarrhea, alopecia, eczematous dermatitis and weight loss that could be reversed by zinc supplementation. Next steps could include using the model to test therapeutics.<br><br><b>SciBX 5(28); doi:10.1038/scibx.2012.743</b><br>Published online July 19, 2012   | Patent and licensing status unavailable                                       | Geiser, J. <i>et al. PLoS Genet.</i> ; published online June 21, 2012; doi:10.1371/journal.pgen.1002766<br><b>Contact:</b> Glen K. Andrews, The University of Kansas Medical Center, Kansas City, Kan.<br>e-mail: <a href="mailto:gandrews@kumc.edu">gandrews@kumc.edu</a>  |

## This week in techniques (continued)

| Approach   | Summary  | Licensing status   | Publication and contact information   |
|--|--|--|---|
| <b>Drug delivery</b>   |  |  |   |
| Adeno-associated virus (AAV) expression of an anti-nicotine antibody   | Persistent expression of an anti-nicotine antibody using an AAV vector could help prevent nicotine addiction. The AAVantiNic vector was generated by engineering AAV to express a Fab fragment of an anti-nicotine mAb. In mice with systemic delivery of nicotine, pretreatment with AAVantiNic led to lower brain nicotine levels and a 47-fold decrease in the ratio of brain to blood nicotine concentrations compared with pretreatment using a control vector. In mice receiving the control vector, systemic nicotine administration decreased blood pressure and heart rate, whereas these effects were blocked in AAVantiNic-treated mice. Next steps include conducting clinical trials and developing an anti-nicotine mAb with higher affinity.<br><br><i>SciBX</i> 5(28); doi:10.1038/scibx.2012.744<br>Published online July 19, 2012  | Patent application filed; available for licensing  | Hicks, M.J. <i>et al. Sci. Transl. Med.</i> ; published online June 27, 2012; doi:10.1126/scitranslmed.3003611<br><b>Contact:</b> Ronald G. Crystal, Weill Cornell Medical College, New York, N.Y.<br>e-mail: <a href="mailto:geneticmedicine@med.cornell.edu">geneticmedicine@med.cornell.edu</a>  |
| <b>Drug platforms</b>  |  |  |   |
| Genetically corrected induced pluripotent stem (iPS) cell-derived mesoangioblasts for limb-girdle muscular dystrophy | Genetically corrected mesoangioblasts derived from iPS cells could be useful for treating limb-girdle muscular dystrophy, which is caused by mutations in the <i>sarcoglycan-<math>\alpha</math></i> (SGCA) gene. Fibroblasts and myoblasts were extracted from patients with limb-girdle muscular dystrophy, reprogrammed into iPS cells, differentiated into mesoangioblast-like cells and then genetically corrected <i>ex vivo</i> using a lentiviral vector encoding normal human SGCA. In a mouse model of limb-girdle muscular dystrophy, transplantation of the genetically corrected mesoangioblasts decreased markers of muscular dystrophy and improved motor performance compared with no transplantation. Next steps could include long-term safety and tumorigenicity studies of the cells in large animal models.<br><br><i>SciBX</i> 5(28); doi:10.1038/scibx.2012.745<br>Published online July 19, 2012 | Patent pending; available for licensing from San Raffaele Hospital<br><b>Contact:</b> Paola Pozzi, San Raffaele Hospital, Milan, Italy<br>e-mail: <a href="mailto:pozzi.paola@hsr.it">pozzi.paola@hsr.it</a> | Tedesco, F.S. <i>et al. Sci. Transl. Med.</i> ; published online June 27, 2012; doi:10.1126/scitranslmed.3003541<br><b>Contact:</b> Francesco Saverio Tedesco, University College London, London, U.K.<br>e-mail: <a href="mailto:f.s.tedesco@ucl.ac.uk">f.s.tedesco@ucl.ac.uk</a><br><b>Contact:</b> Giulio Cossu, same affiliation as above<br>e-mail: <a href="mailto:g.cossu@ucl.ac.uk">g.cossu@ucl.ac.uk</a> |

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