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RET, set, go

By Chris Cain, Senior Writer

Just 15 months after *Ret proto-oncogene* fusions were first identified in 1%–2% of non-small cell lung cancer cases, early data from a Phase II trial of Exelixis Inc.'s Cometriq cabozantinib suggest that blocking the target could be effective in this patient population.¹ At least four additional investigator-initiated trials are seeking to test marketed *Ret* proto-oncogene inhibitors in fusion-positive lung cancer.

In addition, at least seven clinical trials are testing compounds that inhibit other recently identified oncogenic drivers of lung cancer, including amplifications or mutations in *fibroblast growth factor receptors* (*FGFRs*) and mutations in *discoidin domain receptor tyrosine kinase 2* (*DDR2*) (see Table 1, "Selected new targeted therapies in lung cancer" and Box 1, "Squamous smorgasbord").

The rapid move to the clinic validates the prediction made by clinicians and industry researchers that the identification of new oncogenic drivers of lung cancer would spur the development of targeted therapies for new subsets of patients.^{2–5}

In late 2011 and early 2012, four independent teams reported the expression of a KIF5B-*RET* oncogenic fusion protein in non-small cell lung cancer (NSCLC) patient samples and showed that the protein was necessary and sufficient to drive unchecked cellular proliferation.^{6–9} This drew immediate comparisons to the 2007 identification of the EML4-*ALK* oncogenic fusion protein, which drives about 5% of NSCLC cases.¹⁰

A key difference is that when EML4-*ALK* was discovered, there were no marketed anaplastic lymphoma kinase (*ALK*) inhibitors. Pfizer Inc.'s Xalkori crizotinib, a dual inhibitor of c-Met receptor tyrosine kinase and *ALK* and their oncogenic variants, entered the clinic in 2006 and was approved in August 2011 to treat *ALK* fusion-positive lung cancer.⁴

In contrast, *Ret* proto-oncogene (*RET*) kinase is inhibited by multiple marketed nonspecific tyrosine kinase inhibitors, including Cometriq, Nexavar sorafenib, Sutent sunitinib, Caprelsa vandetanib and Iclusig ponatinib.

Cometriq is marketed by Exelixis to treat medullary thyroid cancer (MTC). Nexavar is marketed by Onyx Pharmaceuticals Inc. and Bayer AG to treat liver and renal cancers. Sutent is marketed by Pfizer to treat gastrointestinal stromal tumors (GISTs) and advanced renal cell carcinoma (RCC). Caprelsa is marketed by AstraZeneca plc to treat MTC. Iclusig is marketed by Ariad Pharmaceuticals Inc. to treat certain refractory leukemias.

Naiyer Rizvi, a medical oncologist at Memorial Sloan-Kettering Cancer Center, told SciBX that the availability of these inhibitors made it possible to immediately test whether inhibiting *RET* would have clinical benefit in patients with *RET* fusion-positive lung cancer.

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“The stars aligned to allow us to move this forward so quickly. When the RET fusion was first reported in December 2011, we saw that it fit the profile of other oncogenes that have been described in lung cancer in that it is a tyrosine kinase fusion in patients who have never smoked. We were in a lucky position where there was a drug available that targets VEGF and c-Met but also targets RET, so we contacted Exelixis and they provided us with the compound,” he said.

Rizvi started a Phase II trial of Cometriq at Memorial Sloan-Kettering in July 2012. As of this month, the trial has enrolled 4 patients of a planned 25. He said Exelixis has agreed to provide undisclosed funding for the trial.

In data published in March in *Cancer Discovery*, Rizvi reported that 2 of the first 3 patients enrolled had confirmed partial responses to Cometriq, with a 66% decrease in measurable disease in one patient and a 32% decrease in the other. Both patients have remained progression free on treatment for 4–5 months.

The third patient has had stable disease for eight months on treatment. The fourth patient just started treatment and is too early to evaluate.

Alice Shaw, assistant professor of medicine at **Harvard Medical School** and a thoracic oncologist at **Massachusetts General Hospital**, said these results are comparable to other targeted lung cancer therapies and noted that Xalkori has a response rate of about 60% in ALK-positive lung cancer.

“This is what we would have expected to see in an oncogene-addicted cancer—the preclinical data would predict that patients should be sensitive to a RET inhibitor. We know cabozantinib is a very good RET inhibitor, so it was a very logical step to identify these patients, test an available inhibitor and see a response,” she said.

She compared the frequency of RET mutations to rearrangements of *c-ros proto-oncogene 1 receptor tyrosine kinase (ROS1)*, a tyrosine kinase related to ALK, which are found in 1%–2% of NSCLC cases and predict response to ALK inhibitors including Xalkori. The fusion was first found in lung cancer in 2007, but its prevalence has become more widely appreciated in the last few years as more lung cancer samples have been genetically characterized.

Rizvi said the preliminary result was “sufficiently encouraging to expand the trial to be conducted as a multicenter study as part of the Lung Cancer Mutation Consortium.” The consortium is a **National Cancer Institute** initiative to prospectively examine NSCLC samples from patients and match them to appropriate therapies. It involves 16 cancer centers.

Rizvi said it was reassuring to see the clinical responses because other RET inhibitors were discontinued in lung cancer after poor clinical trial results. For example, Caprelsa missed its primary endpoint in two out of three Phase III lung cancer trials. The trials were completed before the fusion had been identified.

“These data speak to the importance of molecular characterization of NSCLC and identification of appropriate subsets for targeted therapy,” said Rizvi.

“We know cabozantinib is a very good RET inhibitor, so it was a very logical step to identify these patients, test an available inhibitor and see a response.”

—Alice Shaw,
Harvard Medical School

Box 1. Squamous smorgasbord.

Although *Ret proto-oncogene* fusions offer the most promising example for how recent genomic analyses of lung cancer have identified newly actionable oncogenic alterations, additional clinical trials are seeking to validate other new targets, particularly in squamous cell lung cancers. Thus far, none of the ongoing trials have reported results as effective as *Ret proto-oncogene* inhibition.

One area of particular focus is mutations or amplifications of fibroblast growth factor receptors (FGFRs). In 2011, researchers published work suggesting that about 20% of squamous cell lung cancers (SCCs), a subtype of non-small cell lung cancer (NSCLC) associated with smoking, carry amplifications of *FGFR1 (CD331)*.¹³ More recently, activating mutations in FGFR family members have been reported in lung cancer, and last week FGFR oncogenic fusions were reported in a variety of cancers including SCC.^{14,15}

Peter Hammerman, instructor in medicine at **Harvard Medical School** and a thoracic oncologist at the **Dana-Farber Cancer Institute**, is leading a trial of Iclusig ponatinib in patients with lung or head and neck cancer with FGFR alterations.

At the **American Association for Cancer Research (AACR)** meeting this week, **Ariad Pharmaceuticals Inc.** had a poster that showed Iclusig inhibits FGFR1–4 at low nanomolar concentrations and also potentially inhibits the growth of cell lines bearing FGFR alterations, including FGFR1-amplified SCC.

“Ponatinib was selected because it is an FDA-approved agent, and the other high-potency FGFR inhibitors like

BGJ398 and AZD4547 are still in Phase I,” Hammerman said.

BGJ398 is a pan-FGFR inhibitor being developed by **Novartis AG**. The pharma presented data at the AACR meeting last year showing that one SCC patient with amplified FGFR1 had a partial response to the molecule.

AZD4547 is a pan-FGFR inhibitor being developed by AstraZeneca. This week at the AACR meeting, the company presented data showing that one SCC patient with FGFR1 amplification treated with the compound had a partial response that lasted 12 weeks. The patient was 1 of 21 with FGFR1 or FGFR2 (KGFR; CD332) alterations in various cancers that were treated with the compound, and the trial is ongoing.

Roman Thomas, chair of the Department of Translational Genomics at the **University of Cologne**, cautioned that FGFR amplifications in SCC may not be as straightforward to target as gene fusions. “We have data that shows that the biology of FGFR1 amplification is more complicated than originally thought, and we should also keep in mind that [ALK and RET] are more precise genomic alterations compared to amplifications. Unfortunately, though, we do not have response rate data from the AZD4547 or BGJ398 trials yet, so at this point we cannot really draw any conclusions yet.”

Alice Shaw, assistant professor of medicine at Harvard Medical School and a thoracic oncologist at **Massachusetts General Hospital**, agreed that advances in SCC have not been translated as fast as she had hoped. “Squamous has been hard for a number of different reasons. In adenocarcinomas with ALK and ROS1

and RET, it seems like the pace has been quicker.”

In addition to FGFR-targeted therapies, patients with SCC who have activating mutations in *discoidin domain receptor tyrosine kinase 2 (DDR2)* have been enrolled in targeted clinical trials. Hammerman led a 2011 team that found *DDR2* mutations drive 3%–4% of SCC cases and showed that Sprycel dasatinib can inhibit the kinase and block cell proliferation.

Bristol-Myers Squibb Co.'s Sprycel is a tyrosine kinase inhibitor marketed to treat acute lymphoblastic leukemia (ALL) and chronic myelogenous leukemia (CML).

Based on these results, a Dana-Farber investigator started a trial of Sprycel in patients with SCC who have *DDR2* activating mutations. The study was terminated in January for undisclosed safety concerns.

Bruce Johnson, director of the Lowe Center for Thoracic Oncology at Dana-Farber and leader of the aforementioned trial, declined to comment on its termination. Because of its relative lack of activity against *DDR2*,^{3,16} Sprycel was being tested at 140 mg daily orally, which is its highest approved dose.

Bristol-Myers is running its own trial of Sprycel at that dose in patients with lung cancer who have activating *DDR2* mutations. That trial also is enrolling patients with inactivating mutations in BRAF. Last year, a retrospective analysis of patients with lung cancer who received Sprycel identified one patient with an inactivating mutation in BRAF who had a complete response to the compound.¹⁷

Bristol-Myers declined to comment.

—CC

James Vasselli, director of clinical research at AstraZeneca, said the company has conducted a retrospective analysis on lung tumor samples from previous vandetanib trials in NSCLC and has submitted an abstract to the **American Society of Clinical Oncology**. Results were not disclosed.

Gisela Schwab, EVP and CMO of Exelixis, said that based on Rizvi's early results, the company is designing its own trial of Cometriq in RET fusion-positive lung cancer.

“We're continuing the support of this study, but we are also evaluating and are interested in starting a company-initiated trial, and we are talking to various investigators, Dr. Rizvi included,” she said. “The initial signal, even if only collected in a few patients, is strong, and that is one thing to consider when developing a drug—is the effect size going to be convincing enough to make a difference for that small of a patient population.”

Rizvi said it will be important to run a multicenter trial to accrue enough patients to make a convincing case for the clinical benefit of RET inhibition.

Table 1. Selected new targeted therapies in lung cancer. At least 12 clinical trials are testing or plan to test tyrosine kinase inhibitors with activity against recently identified oncogenic drivers of lung cancer in targeted patient populations, including Ret proto-oncogene (RET) fusions, amplifications or mutations in fibroblast growth factor receptors (FGFRs) and discoidin domain receptor tyrosine kinase 2 (DDR2) mutations. Source: *ClinicalTrials.gov* and *University Hospital Medical Information Network*.

Compound	Indication	Status	Sponsor	Company collaborator	Clinical trial record
RET fusions					
Caprelsa vandetanib	Non–small cell lung cancer (NSCLC)	Phase II	Seoul National University Hospital	AstraZeneca plc (LSE:AZN; NYSE:AZN)	NCT01823068
Caprelsa	NSCLC	Phase II	National Cancer Center Hospital East	AstraZeneca	UMIN000010095
Cometriq cabozantinib	NSCLC	Phase II	Memorial Sloan-Kettering Cancer Center	Exelixis Inc. (NASDAQ:EXEL)	NCT01639508
Iclusig ponatinib	NSCLC	Phase II	Massachusetts General Hospital	Ariad Pharmaceuticals Inc. (NASDAQ:ARIA)	NCT01813734
Nexavar sorafenib	NSCLC	Phase II	The Cancer Institute Hospital of JFCR	None	UMIN000007515
DDR2 or BRAF alterations					
Sprycel dasatinib	Squamous cell lung cancer	Phase II ^A	Dana-Farber Cancer Institute	None	NCT01491633
Sprycel	NSCLC or other cancers	Phase II	Bristol-Myers Squibb Co. (NYSE:BMJ)	None	NCT01514864
FGFR amplifications or mutations					
AZD4547 ^B	Breast, squamous lung and stomach cancer	Phase II	The Royal Marsden	AstraZeneca	NCT01795768
AZD4547 plus docetaxel	Squamous cell lung cancer	Phase I/II	Eastern Cooperative Oncology Group	None	NCT01824901
AZD4547	Solid tumors	Phase I	AstraZeneca	None	NCT00979134
Iclusig	Lung and head and neck cancer	Phase II	Dana-Farber	Ariad Pharmaceuticals	NCT01761747
BGJ398 ^B	Solid tumors	Phase I	Novartis AG (NYSE: NVS; SIX:NOVN)	None	NCT01004224
BGJ398	Solid tumors	Phase I (Japan)	Novartis	None	NCT01697605

^ATrial was terminated in January 2013 due to safety concerns. ^BAZD4547 and BGJ398 are selective pan-FGFR inhibitors.

Schwab agreed. “Given the rarity of the fusion gene, in only 1%–2% of NSCLC patients, one has to screen quite a few patients,” she said. “However, you can narrow down the number of patients a little bit by only screening those patients who aren’t *K-Ras* or *EGFR* or *ALK* positive to enrich the population.”

Indeed, Rizvi showed that 5 of 31 patients (16%) screened were positive for RET fusions. He attributed the enriched percentage to the prerequisite that patients had never smoked and were negative for most other known drivers of lung cancer, including mutations in *epidermal growth factor receptor (EGFR)*, *K-Ras*, *neuroblastoma Ras viral (v-Ras) oncogene (NRAS)*, *BRAF*, *HER2 (EGFR2; ErbB2; neu)*, *phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit- α (PIK3CA)*, *MAP kinase kinase 1 (MAP2K1; MEK1)* and *protein kinase B (PKB; PKBA; AKT; AKT1)*, and fusions of *ALK* and *ROS1*.

One of the five RET-positive patients had a previously unseen *tripartite motif containing 33 (TRIM33)-RET* fusion, whereas the other four had *KIF5B-RET* fusions. **Foundation Medicine Inc.** collaborated on screening patients for the mutations.

Schwab said even at a 1%–2% incidence, RET-positive NSCLC cases would still account for a large number of patients.

The **American Cancer Society** estimates that 228,190 cases of lung cancer will be diagnosed in 2013, and about 80%–85% of lung cancers are NSCLC. At the low end, that would translate to about 1,800 RET-positive patients.

RET party

In addition to Exelixis, AstraZeneca and Ariad are now supporting investigator-initiated trials of their compounds in RET fusion–positive lung cancer.

AstraZeneca is working with two groups, one based at **Seoul National University Hospital** in South Korea, which plans to start a Phase II study this year, and one at the **National Cancer Center Hospital East** in Japan, which is enrolling patients.

“Based on the six-plus published papers on RET fusions in NSCLC, key opinion leaders in the field of NSCLC and we at AstraZeneca think that inhibition of RET in NSCLC patients carrying a RET fusion in their tumors has the potential for activity in this disease, so AstraZeneca is interested in evaluating vandetanib in RET fusion–positive NSCLC,” said Vasselli.

Tim Clackson, CSO and president of R&D at Ariad, said the biotech is supporting a multicenter, investigator-initiated trial of Iclusig in RET fusion–positive patients. The study will be run by Massachusetts General Hospital’s Shaw.

Clackson noted that Iclusig has greater potency for RET than other marketed drugs and suggested that the structure of the drug could help combat the emergence of drug resistance.

“Our compound is two orders of magnitude more potent as a RET inhibitor than vandetanib or cabozantinib, at least in terms of IC₅₀ in nonclinical studies,” he said. “Also, by virtue of the design of the compound, we would expect Iclusig to overcome gatekeeper resistance

mutations. It was designed to overcome all known resistance mutations in BCR-ABL because we built structural features into the drug that allow it to bypass gatekeeper mutations, and that ability translates to other kinases.”

In research presented this week at the **American Association for Cancer Research** meeting in Washington, D.C., the company showed that Iclusig has an IC₅₀ value of 0.16 nm for RET kinase and inhibits the growth of KIF5B-RET-transformed cells with an IC₅₀ value of 11 nm. In separate studies published by Exelixis and AstraZeneca, Cometriq had an IC₅₀ value against RET of 5.2 nm, whereas Caprelsa had an IC₅₀ value of 100 nm.^{11,12}

Schwab said the overall target profile of Cometriq may contribute to its efficacy in patients with RET fusion.

Rizvi and Shaw noted that resistance always arises when targeted therapies are used, and they both plan to monitor the emergence of resistance in patients receiving RET inhibitors in their trials.

Rizvi said that despite the high activity of available drugs, there could be a place in the future for more selective RET inhibitors with fewer off-target effects.

Caprelsa, Cometriq and Iclusig each carry black box warnings of toxicity on their labels.

“All three patients in our cabozantinib study have had dose reductions over time for toxicity, and there is significant interest in trying to identify and test more selective inhibitors,” he said.

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- American Association for Cancer Research**, Philadelphia, Pa.
- American Cancer Society**, Atlanta, Ga.
- American Society of Clinical Oncology**, Alexandria, Va.
- Ariad Pharmaceuticals Inc.** (NASDAQ:ARIA), Cambridge, Mass.
- AstraZeneca plc** (LSE:AZN; NYSE:AZN), London, U.K.
- Bayer AG** (Xetra:BAY), Leverkusen, Germany
- Bristol-Myers Squibb Co.** (NYSE:BMJ), New York, N.Y.
- Dana-Farber Cancer Institute**, Boston, Mass.
- Exelixis Inc.** (NASDAQ:EXEL), South San Francisco, Calif.
- Foundation Medicine Inc.**, Cambridge, Mass.
- Harvard Medical School**, Boston, Mass.
- Massachusetts General Hospital**, Boston, Mass.
- Memorial Sloan-Kettering Cancer Center**, New York, N.Y.
- National Cancer Center Hospital East**, Kashiwa, Japan
- National Cancer Institute**, Bethesda, Md.
- Novartis AG** (NYSE:NVS; SIX:NOVN), Basel, Switzerland
- Onyx Pharmaceuticals Inc.** (NASDAQ:ONXX), South San Francisco, Calif.
- Pfizer Inc.** (NYSE:PFE), New York, N.Y.
- Seoul National University Hospital**, Seoul, South Korea
- University of Cologne**, Cologne, Germany

“These data speak to the importance of molecular characterization of NSCLC and identification of appropriate subsets for targeted therapy.”

—Naiyer Rizvi,

Memorial Sloan-Kettering Cancer Center

GSK's electric frontier

By Lev Osherovich, Senior Writer

Today, **GlaxoSmithKline plc** launched an academic partnering program and announced plans for a \$1 million cash prize to spark technology development in the new field of electroceuticals. The pharma's goal is to manipulate nerve impulses to treat a range of diseases in the periphery.

Electroceuticals are an emerging class of therapeutics that consist of nanoscale electrical circuits delivered to specific tissues by implantation or targeted delivery. The class, which includes optogenetic materials and remotely controlled nanoelectronic circuits, aims to control neuronal activity more precisely than is possible with conventional small molecule neuropharmaceuticals.

The [GSK Bioelectronics Exploratory Funding Program](#) will fund up to 40 postdoctoral researchers or their equivalents in up to 20 academic laboratories for 12–18 months to test hypotheses about neurological control of peripheral tissue function. The company did not disclose the specific amount committed to the program.

Kristoffer Famm, VP of bioelectronics R&D at GSK, said the pharma aims to “get in on the ground floor” in miniaturized electrophysiological and optogenetic technologies for manipulating neural activity.

Famm is the corresponding author of a Comment in *Nature* that outlines the funding scheme.¹ The other coauthors are researchers at the **University of Pennsylvania**, **The Feinstein Institute for Medical Research** and the **Massachusetts Institute of Technology**, as well as GSK chairman of R&D Moncef Slaoui.

Famm said the company is looking for new approaches to treat diseases of peripheral tissues in which neurological functions such as endocrine secretion and control of fine muscle activity become impaired. The objective is to develop nanoscale electronic arrays that could be used as implantable therapeutic devices.

“We imagine that we will introduce these electroceuticals at a peripheral nerve close to the organ you want to control,” said Famm. “For example, if you want to affect function of the lung, you would implant in the nerves around the lung.”

What is missing is a detailed understanding of how neurophysiological control becomes compromised in disease and how best to correct these defects. The new funding scheme will help academics gather these data and design appropriate therapeutic strategies.

“In this funding program, we want researchers who have a hypothesis about neural control in a disease process to be able to map those neural components,” said Famm. “The researchers will formulate an exploratory research proposal that they can start up quickly in their lab with one or two postdocs.”

The pharma will help connect grant recipients to other academic researchers who are developing technologies for neural manipulation

such as optogenetic or nanoelectronic arrays. Famm's group will coordinate collaborations between these academic teams through nonexclusive research licensing agreements.

Academics and their institutions will retain IP rights to their discoveries.

Famm said the cash prize will go to a team that meets a grand challenge to be decided after a symposium of grant recipients and GSK representatives this year. The date has not yet been decided.

He added that the GSK-sponsored program will likely use technologies that are being developed as part of the Brain Activity Map (BAM) project and Brain Research through Advancing Innovative Neurotechnologies (BRAIN) initiative.

BAM is a proposed project to measure and model the complete set of neuronal connections in the CNS.² BRAIN is a funding scheme announced last week by the White House to support technology development in neuroscience.

Unlike the BAM and BRAIN projects, which ultimately aim to characterize the function of the normal human CNS, GSK's program will start with animal models to understand the neurophysiological consequences of disease in the periphery.

“The difference between us and BAM is our focus in looking in disease models,” said Famm. “It's an effort to measure the targeted neuronal activity in the disease settings. Knowing the specific neural interface will hopefully allow us to manipulate the disease process.”

Although the goals and timelines of large-scale brain-mapping projects like BAM are far off, Famm thinks that therapeutic manipulation of peripheral disease could be reached in a few years.

“In the periphery, there are already means of recording or even introducing signals into large sets of neurons,” said Famm. “This is used to control prosthetic limbs and is now starting to be done in the central nervous system with electrode arrays and optogenetics. However, we're not yet in a space where we can read and write to the brain.”

The call for proposals opens today.

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COMPANIES AND INSTITUTIONS MENTIONED

The Feinstein Institute for Medical Research, Manhasset, N.Y.
GlaxoSmithKline plc (LSE:GSK; NYSE:GSK), London, U.K.
Massachusetts Institute of Technology, Cambridge, Mass.
University of Pennsylvania, Philadelphia, Pa.

“We imagine that we will introduce these electroceuticals at a peripheral nerve close to the organ you want to control.”
—Kristoffer Famm, GlaxoSmithKline plc

Oncometabolite takedown

By Joanne Kotz, Senior Editor

Agios Pharmaceuticals Inc. has reported the first mutant-selective inhibitors of the metabolic enzymes IDH1 and IDH2 and has shown that the molecules have a therapeutic effect in preclinical cancer models.^{1,2} The company also announced a partnership with **Foundation Medicine Inc.** to develop companion diagnostics to identify patients with cancer who have the mutations.

The metabolic enzymes IDH1 (isocitrate dehydrogenase 1) and IDH2 are somatically mutated in multiple cancers, including about 50%–80% of low-grade gliomas and 9% of acute myelogenous leukemias (AMLs). All of the identified mutations alter one of three arginine residues found in the enzymes' active site.

Isocitrate dehydrogenases catalyze the conversion of isocitrate to α -ketoglutarate (α -KG). In 2009, Agios and academic collaborators reported in *Nature* that the glioma-specific mutation in IDH1 leads to a gain of function in which the mutant enzyme can further convert α -KG to an oncogenic metabolite called (*R*)-2-hydroxyglutarate (*R*-2HG)³ that appears to be the key driver of the cancer-promoting effects of the IDH1 mutation.

In 2010, oncometabolite production was also found to occur with cancer-associated IDH2 mutations.⁴

IDH1 and IDH2 mutations are believed to promote cancer because *R*-2HG can inhibit α -KG-dependent dioxygenases such as histone and DNA methylases, leading to cancer cells that are less differentiated and thus more proliferative than noncancerous cells.

An open question was whether inhibiting the mutant enzymes would have a therapeutic effect.

The Agios-led team has now identified the first mutant-selective inhibitors of each IDH enzyme. An *in vitro* screen of a small molecule library identified initial hits that inhibited the enzyme activity of either mutant target.

Optimization of hits against mutant IDH1 led to the discovery of AGI-5198, which inhibited the R132H mutant of IDH1 with an IC_{50} of 70 nM. It did not inhibit the wild-type enzyme or any of the IDH2 isoforms tested.

Medicinal chemistry optimization of a chemically distinct series led to the identification of AGI-6780, which inhibited the R140Q mutant of IDH2 with nanomolar potency and was selective for mutant enzyme over wild-type IDH2 and other dehydrogenases. Crystallographic studies revealed that the inhibitor bound an allosteric site at the enzyme dimer interface that is not present on IDH1, providing an explanation for the molecule's selectivity.

Next, the researchers tested the inhibitors in preclinical cancer models.

In patient-derived AML cells expressing the R140Q mutant of IDH2, AGI-6780 decreased intracellular and extracellular levels of the oncometabolite *R*-2HG compared with vehicle. The inhibitor induced cancer cell differentiation in the mutant AML cells but not in primary AML cells with wild-type IDH2.

In a xenograft model for R132H-IDH1 glioma, oral AGI-5198 lowered *R*-2HG levels, increased tumor cell differentiation and decreased tumor growth by about 50% compared with vehicle. The inhibitor did not affect the growth of wild-type IDH1 xenografts.

The results of both studies were reported in *Science*.

Clinical setup

Agios is continuing preclinical development of mutant-selective IDH1 and IDH2 inhibitors and hopes to start Phase I testing for both programs over the next year or two. The biotech also wants to explore the effects of mutant IDH inhibitors in additional cancers.

"We are continuing to look at preclinical animal models, focusing a lot on solid tumor models in which *IDH1* is mutated, particularly chondrosarcoma and cholangiocarcinoma," said Katharine Yen, director of biology at Agios.

CSO Scott Biller added, "There is no standard of care for either indication, and so we see great opportunity there."

Biller said the reported molecules are tool compounds. He declined to disclose whether the company has identified clinical candidates but noted that "we've made a lot of progress in both programs and expect to be in the clinic in 12–24 months. Our intention is to only test the compounds in patients with IDH mutations."

Biller added that the initial indications are not disclosed.

Agios also will continue preclinical "exploratory studies to better understand the downstream biology" induced by the oncometabolite and the mutant-selective inhibitors, said Biller.

The company intends to monitor the downstream pathways during Phase I

testing. "We can look, for instance, at the actual cytology of the cells in AML and at histone modifications and changes in gene expression in glioma and figure out which of these are most meaningful for response," said Yen.

In the Phase I trials, the company plans to use *R*-2HG, the direct product of mutant IDH enzymatic activity, as the primary marker of target engagement. Biller noted that the oncometabolite could provide an early marker of drug efficacy.

"Studies in collaboration with MGH [Massachusetts General Hospital] looking at 2HG as a biomarker in AML showed that when you treat patients with standard of care, 2HG levels go down as the AML burden decreases and come up with relapse. Thus, 2HG is potentially also a marker for response and relapse," he said.

The partnership with Foundation Medicine may also help refine a patient selection strategy. In Phase I studies, Foundation Medicine's genomic profiling will be used to determine if there are oncogenic alterations beyond IDH mutations that correlate with response, according to Biller and Yen.

(Continues on p. 8)

"We are continuing to look at preclinical animal models, focusing a lot on solid tumor models in which *IDH1* is mutated, particularly chondrosarcoma and cholangiocarcinoma."

**—Katharine Yen,
Agios Pharmaceuticals Inc.**

RaPID results

By Chris Cain, Senior Writer

A Japanese team has provided new structural insights into the function of a conserved class of drug transporters and has identified cyclic peptide inhibitors of one such protein.¹ The researchers are now collaborating with **PeptiDream Inc.** to develop compounds with improved drug-like properties that hit medically relevant targets.

The multidrug and toxic compound extrusion (MATE) class of transporters exports diverse cationic chemical substrates and is conserved across all domains of life. Although the physiological roles of MATEs are still being worked out in humans and other organisms, in the lab they are capable of exporting antibiotics in multidrug-resistant pathogenic bacteria including *Neisseria gonorrhoea* and *Staphylococcus aureus*, though their contribution to clinically relevant drug resistance remains unclear.

MATEs import Na⁺ or H⁺ as they export their substrate. The first crystal structure of a MATE transporter was solved in 2010, but its resolution did not allow a complete understanding of the molecular mechanism by which ion import drives drug export.²

To flesh out the mechanism, researchers at **The University of Tokyo** and the **RIKEN Advanced Science Institute** sought to capture high-resolution structures of a MATE by using a structurally stable homolog from the thermophile *Pyrococcus furiosus*. The team crystalized the transporter in multiple conformations, including in complexes with a fluoroquinolone antibiotic substrate, norfloxacin, and with newly developed macrocyclic inhibitors of the target.

The inhibitors were developed using the technology platform known as random, nonstandard peptide integrated discovery (RaPID).³ RaPID uses *in vitro* mRNA display to synthesize and screen against trillions of peptides that contain a mix of natural and unnatural amino acids. The system enabled the identification of thioether-macrocyclic peptide inhibitors that blocked *P. furiosus* MATE substrate transport at low micromolar concentrations.

“Our inhibitory cyclic peptide paves the way toward the development of efficient inhibitors against previously undruggable MATE transporters.”

— Osamu Nureki,
The University of Tokyo

RaPID was developed in the lab of Hiroaki Suga, a co-corresponding author of the study who is the cofounder and external executive officer of PeptiDream, which is commercializing the technology.⁴ Suga also is a professor in the Department of Chemistry at the University of Tokyo.

Together, the series of structures showed that the transporter adopts two distinct outward-facing conformations and suggested how a substrate is extruded by the transporter upon H⁺ import. Like most transport proteins, MATEs bind intracellular substrates in inward-facing conformations, then transition to outward-facing conformations to release their substrates.

Co-corresponding author Osamu Nureki, professor in the Department of Biochemistry and Biophysics at the University of Tokyo, told *SciBX* that the export mechanism is the most important new piece of information provided by these structures.

Hendrick van Veen, senior lecturer in the Department of Pharmacology at the **University of Cambridge**, agreed. “One key finding of the current structure is that it provides new insights into the question of how substrate transport is coupled to the movement of protons,” he said. “Based on [the MATEs’] structures, the researchers propose that when a proton binds to the MATE transporter, it switches the conformation to allow the dissociation of the toxin molecule into the extracellular environment.”

Geoffrey Chang, whose team crystalized the first MATE transporter in 2010, said the resolution of the new transporter structures was critical to enabling the new insights. Chang’s structure of the *Vibrio cholera* Na⁺ MATE transporter NorM was resolved at 3.65 Å. The series of structures presented in the new work range from 2.1–3 Å.

Chang is a professor of pharmacology at the **University of California, San Diego**.

Nureki now plans to conduct studies on more therapeutically relevant MATE proteins, including those from pathogenic bacteria and humans, and to solve the structures of the transporters complexed with specific inhibitory peptides. “Our inhibitory cyclic peptide paves the

(Continues on p. 9)

(Continued from “Oncometabolite takedown,” p. 7)

The company did not disclose the IP status of the programs. Agios’ IDH1 and IDH2 programs are partnered with **Celgene Corp.** Under a 2010 deal, Celgene received an option to license selected Agios compounds after Phase I testing in exchange for \$130 million up front and up to \$120 million in milestones per program, plus royalties. Agios will retain certain co-development and marketing rights.

Kotz, J. *SciBX* 6(14); doi:10.1038/scibx.2013.328
Published online April 11, 2013

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Contact: Ingo K. Mellinshoff, Memorial Sloan-Kettering Cancer Center, New York, N.Y.
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COMPANIES AND INSTITUTIONS MENTIONED

Agios Pharmaceuticals Inc., Cambridge, Mass.
Celgene Corp. (NASDAQ:CELG), Summit, N.J.
Foundation Medicine Inc., Cambridge, Mass.
Massachusetts General Hospital, Boston, Mass.

way toward the development of efficient inhibitors against previously undruggable MATE transporters,” he said. “Unfortunately, because traditional antibiotics are small and readily transported out by MATEs, it was difficult to discover potent inhibitors. The thioether-macrocyclic peptides are the right molecular size to fit into the active pocket of MATE and effectively clog it and inhibit its function.”

RaPID results

Suga said the team plans to use RaPID to optimize inhibitory peptides with unnatural and D-amino acids, which are more resistant to proteases found in the blood and can increase cell permeability compared with unmodified L-amino acids.

van Veen said he was impressed that the cyclic peptides were able to block transport without entering the cell. “The researchers have identified a new type of inhibitor for MATE that acts by binding to outward-facing MATE from the exterior of the cell. This represents a very promising approach to inhibit multidrug transporters in a clinical setting because the inhibitor does not need to enter the cell to exert its action,” he said.

van Veen and Chang both said the next key advance for understanding MATE transport will come from solving the structure of an inward-facing MATE transporter.

Robert Stavenger, group leader at **GlaxoSmithKline plc** and project coordinator for TRANSLOCATION, an **Innovative Medicines Initiative** program studying drug transport in Gram-negative bacteria, said the work provides a promising model of MATE transporter action. However, he expressed concern that MATEs have not yet been linked to clinically relevant drug resistance in bacteria.

“MATE transporters have been implicated as a potential mechanism for resistance against *S. aureus* but mostly in the laboratory setting. It doesn’t seem that MATE transporters are strongly involved in clinically relevant antibacterial resistance at this time. As such, I would consider them less important than, for example, NorA in *S. aureus* or the various resistance-nodulation–cell division (RND) efflux systems in Gram-negative bacteria,” he said.

NorA is a member of a distinct class of drug transporters and contributes to fluoroquinolone resistance in *S. aureus*, whereas members of the RND class of transporters have been linked to resistance in bacteria including the emerging Gram-negative pathogen *Acinetobacter baumannii*.

Suga said the concern is valid and that it is challenging to combat antibiotic resistance by targeting only one transporter because bacteria encode numerous families of drug efflux pumps. He did say the study provides proof of concept for a strategy to identify cyclic peptide inhibitors against other families of drug transporters.

Nureki said the group now plans to expand its studies beyond MATEs and conduct studies of additional efflux pumps, including ATP-binding cassette transporters associated with drug resistance.

Results were published in *Nature*. Patent applications have been filed by the University of Tokyo and are exclusively licensed to PeptiDream.

Cain, C. *SciBX* 6(14); doi:10.1038/scibx.2013.329

Published online April 11, 2013

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e-mail: hsuga@chem.s.u-tokyo.ac.jp
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GlaxoSmithKline plc (LSE:GSK; NYSE:GSK), London, U.K.
Innovative Medicines Initiative, Brussels, Belgium
PeptiDream Inc., Tokyo, Japan
RIKEN Advanced Science Institute, Saitama, Japan
University of California, San Diego, La Jolla, Calif.
University of Cambridge, Cambridge, U.K.
The University of Tokyo, Tokyo, Japan

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				
Acute myelogenous leukemia (AML)	Isocitrate dehydrogenase 2 (IDH2)	<p>Patient sample and <i>in vitro</i> studies suggest mutant-selective IDH2 inhibitors could help treat patients with IDH2-mutant AML. In <i>in vitro</i> assays, AGI-6780 inhibited mutant IDH2 with nanomolar potency and selectivity over the wild-type enzyme. In primary human AML cells with mutant IDH2, AGI-6780 decreased levels of the (<i>R</i>)-enantiomer of 2-hydroxyglutarate (2-HG), an oncometabolite produced specifically by the mutant enzyme, and increased leukemic cell differentiation compared with vehicle. Next steps include further preclinical development of mutant IDH2 inhibitors in preparation for clinical trials in patients who have IDH2-mutant AML.</p> <p>Agios Pharmaceuticals Inc. has preclinical programs targeting IDH1 and IDH2 in cancers with mutations in the metabolic enzymes (see Oncometabolite takedown, page 7).</p> <p>SciBX 6(14); doi:10.1038/scibx.2013.330 Published online April 11, 2013</p>	Patent applications filed; partnered with Celgene Corp.	<p>Wang, F. <i>et al. Science</i>; published online April 4, 2013; doi:10.1126/science.1234769</p> <p>Contact: Katharine E. Yen, Agios Pharmaceuticals Inc., Cambridge, Mass. e-mail: katharine.yen@agios.com</p>
Brain cancer	H3 histone family 3A (H3.3A; H3F3A); histone cluster 1 H3b (HIST1H3B); polycomb repressive complex 2 (PRC2)	<p><i>In vitro</i> and cell culture studies identified gain-of-function mutations in H3F3A and HIST1H3B that could be targeted to treat pediatric glioblastoma. The K27M mutation in either H3F3A or HIST1H3B is found in almost 80% of diffuse intrinsic pontine gliomas (DIPGs), a type of pediatric brain cancer. In a series of cell culture and <i>in vitro</i> assays, the K27M mutation was identified as a gain-of-function mutation that conferred the ability to inhibit PRC2. Next steps could include screening for compounds that inhibit the DIPG-associated mutant proteins.</p> <p>SciBX 6(14); doi:10.1038/scibx.2013.331 Published online April 11, 2013</p>	Patent and licensing status unavailable	<p>Lewis, P.W. <i>et al. Science</i>; published online March 28, 2013; doi:10.1126/science.1232245</p> <p>Contact: C. David Allis, The Rockefeller University, New York, N.Y. e-mail: alliscd@rockefeller.edu</p>
Brain cancer	Isocitrate dehydrogenase 1 (IDH1)	<p>Mouse and <i>in vitro</i> studies suggest inhibiting mutant IDH1 could help treat IDH1-mutant gliomas. <i>In vitro</i>, AGI-5198 inhibited mutant IDH1 with an IC₅₀ value of 70 nM without also inhibiting wild-type IDH1 at detectable levels. In a mouse xenograft model for human glioma, AGI-5198 decreased levels of the (<i>R</i>)-enantiomer of 2-hydroxyglutarate (2-HG), an oncometabolite specifically produced by the mutant enzyme, and decreased tumor growth compared with vehicle. Next steps include conducting further preclinical development of mutant-selective IDH1 inhibitors and testing the effects of the inhibitors in other IDH1-mutant solid tumors.</p> <p>Agios Pharmaceuticals Inc. has preclinical programs targeting IDH1 and IDH2 in cancers with mutations in the metabolic enzymes (see Oncometabolite takedown, page 7).</p> <p>SciBX 6(14); doi:10.1038/scibx.2013.332 Published online April 11, 2013</p>	Patent applications filed; partnered with Celgene Corp.	<p>Rohle, D. <i>et al. Science</i>; published online April 4, 2013; doi:10.1126/science.1236062</p> <p>Contact: Katharine E. Yen, Agios Pharmaceuticals Inc., Cambridge, Mass. e-mail: katharine.yen@agios.com</p> <p>Contact: Ingo K. Mellinshoff, Memorial Sloan-Kettering Cancer Center, New York, N.Y. e-mail: mellingi@mskcc.org</p>
Cancer	Discoidin domain receptor tyrosine kinase 1 (DDR1)	<p>Rat and <i>in vitro</i> studies identified inhibitors of DDR1 that could help treat cancer. In <i>in vitro</i> assays, compounds from a class of 3-(2-(pyrazolo[1,5-<i>a</i>]pyrimidin-6-yl)ethyl)benzamides inhibited DDR1 with low nanomolar potency. In a panel of human cancer cell lines with high DDR1 expression, the lead molecules inhibited cell growth. In rats, the inhibitors showed high oral bioavailability and good pharmacokinetics. Next steps include studying the molecules in animal models of cancer.</p> <p>SciBX 6(14); doi:10.1038/scibx.2013.333 Published online April 11, 2013</p>	Patent application filed; available for licensing	<p>Ding, K. <i>et al. J. Med. Chem.</i>; published online March 22, 2013; doi:10.1021/jm301824k</p> <p>Contact: Yong Xu, Chinese Academy of Sciences, Guangzhou, China e-mail: tu_zhengchao@gibh.ac.cn</p> <p>Contact: Ke Ding, same affiliation as above e-mail: ding_ke@gibh.ac.cn</p>

This week in therapeutics

Indication	Target/marker/pathway	Summary	Licensing status	Publication and contact information
Cancer	Tankyrase TRF1-interacting ankyrin-related ADP-ribose polymerase (TNKS); TNKS2	<i>In vitro</i> and mouse studies identified a TNKS and TNKS2 dual inhibitor that could be useful for treating cancer. TNKS and TNKS2 regulate multiple cancer-associated pathways. <i>In vitro</i> , the lead molecule selectively inhibited TNKS and TNKS2 with IC ₅₀ values of 46 nM and 25 nM, respectively. In mice, the lead molecule showed good bioavailability following intraperitoneal and oral administration. Next steps include developing a strategy to stratify patients with cancer based on their expression of TNKS and TNKS2. SciBX 6(14); doi:10.1038/scibx.2013.334 Published online April 11, 2013	Patent application filed covering composition of matter; licensing negotiations ongoing	Voronkov, A. <i>et al. J. Med. Chem.</i> ; published online March 11, 2013; doi:10.1021/jm4000566 Contact: Stefan Krauss, Oslo University Hospital, Oslo, Norway e-mail: stefan.krauss@rr-research.no Contact: Jens P. Morth, same affiliation as above e-mail: j.p.morth@ncmm.uio.no Contact: Jo Waaler, same affiliation as above e-mail: jo.waaler@rr-research.no
Non-small cell lung cancer (NSCLC)	Ret proto-oncogene (RET); KIF5B-RET oncogenic fusion protein	Preliminary results from an investigator-initiated Phase II trial suggest small molecule RET inhibitors could help treat RET fusion-positive lung cancers. Last year, KIF5B-RET fusions were identified in 1%–2% of patients with NSCLC. In three RET fusion-positive patients treated with Cometriq cabozantinib, two had a confirmed partial response and the third had stable disease. Next steps include expanding the clinical trial and continuing patient follow-up. Exelixis Inc. markets Cometriq, a small molecule c-Met receptor tyrosine kinase and VEGF inhibitor that also inhibits RET, to treat medullary thyroid cancer. Ariad Pharmaceuticals Inc.'s Iclusig ponatinib, a pan-BCR-ABL tyrosine kinase inhibitor that also inhibits RET, is in a separate investigator-led Phase II trial to treat RET fusion-positive NSCLC (see RET, set, go, page 1). SciBX 6(14); doi:10.1038/scibx.2013.335 Published online April 11, 2013	Patent and licensing status not applicable	Drilon, A. <i>et al. Cancer Discov.</i> ; published online March 26, 2013; doi:10.1158/2159-8290.CD-13-0035 Contact: Naiyer A. Rizvi, Memorial Sloan-Kettering Cancer Center, New York, N.Y. e-mail: rizvin@mskcc.org
Ovarian cancer	<i>HNF1 homeobox B</i> (<i>HNF1B</i>)	Patient studies suggest genetic and epigenetic variation in <i>HNF1B</i> could be useful for the classification and prognosis of ovarian cancers. In ovarian tumor samples, epigenetic DNA analysis showed that the <i>HNF1B</i> promoter region was methylated in 42% of serous tumors, whereas methylation levels were 0% in clear cell ovarian tumors. In samples from 44,308 subjects, genetic analysis showed that the rs7405776 SNP in <i>HNF1B</i> was associated with increased risk for invasive serous ovarian cancer, whereas the rs11651755 SNP in <i>HNF1B</i> was associated with decreased risk for clear cell ovarian cancer. Next steps could include developing an assay to classify ovarian cancers based on genetic and epigenetic variation in <i>HNF1B</i> . SciBX 6(14); doi:10.1038/scibx.2013.336 Published online April 11, 2013	Patent and licensing status unavailable	Shen, H. <i>et al. Nat. Commun.</i> ; published online March 27, 2013; doi:10.1038/ncomms2629 Contact: Celeste Leigh Pearce, University of Southern California Norris Comprehensive Cancer Center, Los Angeles, Calif. e-mail: cpearce@usc.edu Contact: Ellen L. Goode, Mayo Clinic, Rochester, Minn. e-mail: egoode@mayo.edu
Sarcoma	Focal adhesion kinase (FAK)	Cell culture and mouse studies suggest inhibiting FAK could help treat Ewing's sarcoma. In Ewing's sarcoma cell lines, a small molecule FAK inhibitor blocked cell viability with an average IC ₅₀ value of 2.4 μM. In a mouse model for Ewing's sarcoma, small hairpin RNA or a small molecule inhibitor against FAK decreased tumor growth compared with control shRNA or vehicle. Next steps include testing FAK inhibitors in combination with other therapies and examining the role of FAK in metastasis. CureFAKtor Pharmaceuticals LLC's CFAK-C4, a FAK and VEGF receptor 3 (FLT4; VEGFR-3) inhibitor, is in preclinical development for pancreatic cancer. Verastem Inc.'s VS-6063, a FAK inhibitor in-licensed from Pfizer Inc., is in Phase I testing to treat ovarian cancer. Verastem's VS-4718, a FAK inhibitor in-licensed from Poniard Pharmaceuticals Inc., is in preclinical development to treat cancer. SciBX 6(14); doi:10.1038/scibx.2013.337 Published online April 11, 2013	Unpatented; licensing status not applicable	Crompton, B.D. <i>et al. Cancer Res.</i> ; published online March 27, 2013; doi:10.1158/0008-5472.CAN-12-1944 Contact: Kimberly Stegmaier, Dana-Farber Cancer Institute, Boston, Mass. e-mail: kimberly_stegmaier@dfci.harvard.edu

This week in therapeutics

Indication	Target/marker/ pathway	Summary	Licensing status	Publication and contact information
Infectious disease				
Dengue fever	Dengue NS3 protease; dengue NS2B protein	<i>In vitro</i> studies suggest a new dengue protease complex could help guide the development of new antivirals to treat dengue fever. A dengue protease construct in which NS2B and NS3 are linked has been previously used to provide crystal structure information but gives limited NMR data. Coexpressing the NS2B cofactor region and the NS3 protease domain in <i>Escherichia coli</i> generated an enzymatically active, unlinked dengue protease complex that yielded well-resolved NMR data. Next steps could include using the new NMR data for structure-based drug design. SciBX 6(14); doi:10.1038/scibx.2013.338 Published online April 11, 2013	Unpatented; unlicensed	Kim, Y.M. <i>et al. J. Biol. Chem.</i> ; published online March 19, 2013; doi:10.1074/jbc.M112.442723 Contact: Thomas H. Keller, Agency for Science, Technology and Research (A*STAR), Singapore e-mail: thkeller@etc.a-star.edu.sg Contact: CongBao Kang, same affiliation as above e-mail: cbkang@etc.a-star.edu.sg Contact: Qing-Yin Wang, Novartis Institute for Tropical Diseases, Singapore e-mail: qing_yin.wang@novartis.com
Inflammation				
Inflammation	F-box protein 3 (FBXO3)	Patient sample and mouse studies suggest FBXO3 inhibitors could be used to treat inflammation caused by infectious diseases. In 8 of 60 human peripheral blood mononuclear cell (PBMC) samples, a loss-of-function FBXO3 mutation was identified, which led to lower cytokine production in response to lipopolysaccharide (LPS) than wild-type FBXO3. In a mouse model for pneumonia, small hairpin RNA-mediated knockdown of FBXO3 decreased markers of inflammation and increased survival compared with no knockdown. In the model, the FBXO3-targeting benzathine derivative BC-1215 decreased markers of inflammation compared with vehicle. Next steps include evaluating the pharmacokinetics and toxicity of BC-1215 and related molecules. SciBX 6(14); doi:10.1038/scibx.2013.339 Published online April 11, 2013	Patent application filed; available for licensing	Chen, B.B. <i>et al. Nat. Immunol.</i> ; published online March 31, 2013; doi:10.1038/ni.2565 Contact: Rama K. Mallampalli, University of Pittsburgh, Pittsburgh, Pa. e-mail: mallampallirk@upmc.edu
Inflammation	Sirtuin 6 (SIRT6); tumor necrosis factor- α (TNF- α)	<i>In vitro</i> and cell culture studies suggest inhibiting SIRT6 could help treat inflammation by reducing TNF- α secretion. <i>In vitro</i> , SIRT6 hydrolyzed long-chain fatty acid-modified histones and TNF- α about 100–200-fold more efficiently than it deacetylated histones. In cultured cells, small hairpin RNA against SIRT6 decreased levels of long-chain fatty acid-modified TNF- α and decreased secretion of the protein compared with control shRNA. Next steps include developing SIRT6-specific inhibitors and identifying other proteins regulated by this mechanism. SciBX 6(14); doi:10.1038/scibx.2013.340 Published online April 11, 2013	Patent application filed; available for licensing	Jiang, H. <i>et al. Nature</i> ; published online April 4, 2013; doi:10.1038/nature12038 Contact: Hening Lin, Cornell University, Ithaca, N.Y. e-mail: h1379@cornell.edu Contact: Quan Hao, The University of Hong Kong, Hong Kong, China e-mail: qhao@hku.hk
Neurology				
Fragile X syndrome	Cannabinoid CB ₁ receptor (CNR1); CNR2	Mouse studies suggest blocking the endocannabinoid system could help treat fragile X syndrome. In mouse models for fragile X syndrome, the small molecule CNR1 antagonist rimonabant decreased cognitive impairment and susceptibility to noise-induced seizures compared with vehicle. In the mouse model, a research-grade small molecule CNR2 antagonist decreased anxiolytic behaviors compared with vehicle. Next steps include seeking a partner to carry out clinical studies and characterizing the effects of other molecules that antagonize the endocannabinoid system in animals. Sanofi discontinued marketing Acomplia/Zimulti rimonabant to treat obesity in 2007 due to psychiatric side effects. At least five companies have CNR1 and/or CNR2 antagonists in Phase I testing or earlier to treat endocrine/metabolic, hepatic or neurological indications. SciBX 6(14); doi:10.1038/scibx.2013.341 Published online April 11, 2013	Patent application filed; available for licensing	Busquets-Garcia, A. <i>et al. Nat. Med.</i> ; published online March 31, 2013; doi:10.1038/nm.3127 Contact: Andrés Ozaita, Pompeu Fabra University, Barcelona, Spain e-mail: andres.ozaita@upf.edu

This week in therapeutics

Indication	Target/marker/ pathway	Summary	Licensing status	Publication and contact information
Insomnia	Orexin 1 receptor (HCRTR1; OX1R); HCRTR2 (OX2R)	Rat and nonhuman primate studies suggest antagonizing orexin receptors could help treat insomnia with fewer cognitive side effects than marketed drugs that modulate GABA receptors. In rats and nonhuman primates, an orexin receptor antagonist induced sleep at concentrations that did not significantly decrease cognition in object recognition tests, whereas a series of compounds that modulate GABA receptors did decrease cognition. Next steps include clinical studies to evaluate the effect of orexin antagonists on cognition. An NDA for Merck & Co. Inc.'s suvorexant, a dual orexin receptor antagonist, will be discussed by an FDA advisory committee on May 22, 2013. At least seven companies market GABA receptor modulators to treat insomnia. SciBX 6(14); doi:10.1038/scibx.2013.342 Published online April 11, 2013	Patents pending; licensing status unavailable	Uslaner, J.M. <i>et al. Sci. Transl. Med.</i> ; published online April 3, 2013; doi:10.1126/scitranslmed.3005213 Contact: Jason M. Uslaner, Merck & Co. Inc., West Point, Pa. e-mail: jason_uslaner@merck.com
Pain	μ -Opioid receptor (OPRM1; MOR)	SAR studies identified synthetic peptide analogs of endomorphin-1 that could be useful for treating pain. <i>In vitro</i> SAR studies identified a series of unnatural amino acid-bearing endomorphin-1 derivatives that agonized OPRM1 at subpicomolar concentrations. In an <i>in vitro</i> assay, the lead compound in the series had about a 35-fold longer half-life than natural endomorphin-1. In a mouse pain assay, the lead compound showed more potent analgesic effects than morphine. Next steps include further optimizing the compounds and conducting preclinical safety studies. SciBX 6(14); doi:10.1038/scibx.2013.343 Published online April 11, 2013	Patent pending; unavailable for licensing	Liu, X. <i>et al. J. Med. Chem.</i> ; published online March 11, 2013; doi:10.1021/jm400195y Contact: Rui Wang, Lanzhou University, Lanzhou, China e-mail: wangrui@lzu.edu.cn
Renal disease				
Polycystic kidney disease (PKD)	Polycystic kidney disease 1 (PKD1)	Mouse studies suggest inhibiting glycolysis could help treat autosomal dominant PKD. In <i>Pkd1</i> -deficient mice and in cysts from patients with PKD, expression of genes involved in glycolysis was greater than that in wild-type mice and minimally cystic human tissues, respectively. In the PKD mouse model, 2-deoxyglucose, a glucose analog that inhibits glycolysis, decreased kidney cyst numbers and kidney volume and weight compared with vehicle. Next steps include additional animal studies. SciBX 6(14); doi:10.1038/scibx.2013.344 Published online April 11, 2013	Patent application filed; available for licensing	Rowe, I. <i>et al. Nat. Med.</i> ; published online March 24, 2013; doi:10.1038/nm.3092 Contact: Alessandra Boletta, San Raffaele Scientific Institute, Milan, Italy e-mail: boletta.alessandra@hsr.it Contact: Giovanna Musco, same affiliation as above e-mail: musco.giovanna@hsr.it

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			
Panel of peptoid ligands of aquaporin-4 (AQP4) autoantibodies for diagnosing neuromyelitis optica (NMO)	A panel of peptoid ligands that bind AQP4 autoantibodies could be useful for diagnosing NMO. A library of 100,000 peptoid compounds was synthesized on beads and subsequently screened for their ability to bind AQP4 autoantibodies, which are a hallmark of NMO. The 10 lead hits from the screen were used to develop a fluorescence assay to analyze patient sera. In serum samples from healthy controls and patients who have NMO, the assay correctly identified 14 of the 15 samples that came from patients who have NMO and distinguished them from sera samples taken from patients with multiple sclerosis (MS), lupus, Alzheimer's disease (AD) or narcolepsy. Next steps include identifying peptoid ligands with increased affinity for AQP4 autoantibodies.	Patented; licensing status undisclosed	Raveendra, B.L. <i>et al. Chem. Biol.</i> ; published online March 21, 2013; doi:10.1016/j.chembiol.2012.12.009 Contact: Thomas Kodadek, Scripps Florida, Jupiter, Fla. e-mail: kodadek@scripps.edu
	SciBX 6(14); doi:10.1038/scibx.2013.345 Published online April 11, 2013		
Yeast chemical genetic screen for inhibitors of human telomerase	A yeast chemical genetic screening assay for small molecule inhibitors of human telomerase could help identify new leads to treat telomerase-positive cancers. The assay identified small molecules that could restore growth in an engineered strain of yeast that undergoes inducible growth arrest in the presence of human telomerase. In a library of 678 compounds, the screening assay identified 8 such molecules. In a series of <i>in vitro</i> assays, three of the eight identified molecules were shown to inhibit human telomerase. Next steps could include testing the molecules in telomerase-positive cancer cell lines and screening a larger compound library in the yeast-based assay.	Patent and licensing status undisclosed	Wong, L.H. <i>et al. Chem. Biol.</i> ; published online March 21, 2013; doi:10.1016/j.chembiol.2012.12.008 Contact: Lea Harrington, University of Montreal, Montreal, Quebec, Canada e-mail: lea.harrington@umontreal.ca
	SciBX 6(14); doi:10.1038/scibx.2013.346 Published online April 11, 2013		
Disease models			
Induced neuroblastoma stem cells	An induced stem cell-like neuroblastoma cell line could be useful for studying the cancer. In culture, treatment of a standard neuroblastoma cell line with inhibitors of DNA methylation and histone deacetylation led to long-term expression of stem cell-associated markers. Mice grafted with these stem cell-like neuroblastoma cells showed higher rates of tumor formation and metastasis than mice receiving a standard neuroblastoma cell line. Next steps could include testing therapeutic candidates against the induced neuroblastoma stem cells.	Patent and licensing status undisclosed	Ikegaki, N. <i>et al. Proc. Natl. Acad. Sci. USA</i> ; published online March 11, 2013; doi:10.1073/pnas.1118262110 Contact: Xao X. Tang, University of Illinois at Chicago, Chicago, Ill. e-mail: xaotang@uic.edu
	SciBX 6(14); doi:10.1038/scibx.2013.347 Published online April 11, 2013		
Mammalian cell and fruit fly models for neurodegeneration induced by GGGGCC repeats	Mammalian neuronal cells and fruit flies that express GGGGCC repeats could be useful as models to study disease pathology and evaluate therapeutic candidates to treat amyotrophic lateral sclerosis (ALS) and frontotemporal dementia (FTD). Mammalian neuronal cells and neuronal tissues of fruit flies were engineered to express expanded GGGGCC repeats, which have been associated with ALS and FTD. In these models, expression of the repeat was sufficient to cause degeneration of neuronal cells, and overexpression of purine-rich element binding protein A (PURA), which binds to the GGGGCC repeats, led to decreased degeneration in neuronal cells compared with overexpression of a control protein. Next steps include conducting additional studies to validate the toxicity of the GGGGCC repeats and studying the distribution of PURA in mouse models.	Models unpatented; available for licensing	Xu, Z. <i>et al. Proc. Natl. Acad. Sci. USA</i> ; published online April 3, 2013; doi:10.1073/pnas.1219643110 Contact: Peng Jin, Emory University School of Medicine, Atlanta, Ga. e-mail: peng.jin@emory.edu Contact: Thomas S. Wingo, same affiliation as above e-mail: thomas.wingo@emory.edu
	SciBX 6(14); doi:10.1038/scibx.2013.348 Published online April 11, 2013		

This week in techniques

Approach	Summary	Licensing status	Publication and contact information
Transgenic rat model for Alzheimer's disease (AD)	<p>A transgenic rat model for AD could help identify new therapeutic candidates to treat AD. The rats were engineered to express AD-associated mutant human amyloid precursor protein (APP) and presenilin 1 (PSEN1; PS1). The rats showed progressive accumulation and deposition of β-amyloid ($A\beta$) and microtubule-associated protein-τ (MAPT; TAU; FTDP-17) pathology in the brain and had progressive loss of neurons. Next steps include making the rat model available to the research community.</p> <p>SciBX 6(14); doi:10.1038/scibx.2013.349 Published online April 11, 2013</p>	Model unpatented; available for licensing	<p>Cohen, R.M. <i>et al. J. Neurosci.</i>; published online April 10, 2013; doi:10.1523/JNEUROSCI.3672-12.2013 Contact: Terrence Town, Cedars-Sinai Medical Center, Los Angeles, Calif. e-mail: terrence.town@csmc.edu Contact: Robert M. Cohen, Emory University, Atlanta, Ga. e-mail: robert.m.cohen@emory.edu</p>
Drug platforms			
Antibody regions required for broadly neutralizing HIV antibody activity	<p><i>In vitro</i> and structural studies identified new regions of antibodies against HIV that could contribute to their broadly neutralizing activity. Somatic mutations were found more frequently in a panel of broadly neutralizing anti-HIV antibodies than in a panel of antibodies with more limited neutralizing activity. In broadly neutralizing antibodies, mutations in IgG structural framework regions were identified that do not make contact with HIV antigens but are still required for the broadly neutralizing activity. Next steps could include analyzing these regions when assessing responses to HIV vaccines.</p> <p>SciBX 6(14); doi:10.1038/scibx.2013.350 Published online April 11, 2013</p>	Patent and licensing status unavailable	<p>Klein, F. <i>et al. Cell</i>; published online March 28, 2013; doi:10.1016/j.cell.2013.03.018 Contact: Michel C. Nussenzweig, The Rockefeller University, New York, N.Y. e-mail: nussen@mail.rockefeller.edu</p>
Bacteriophage T4 co-delivery of DNA and proteins for prime-boost vaccines	<p>Cell culture and mouse studies suggest co-delivery of DNA and proteins with bacteriophage T4 could be useful as a vaccine. In mice, intramuscular injection with bacteriophage T4 heads engineered to package the <i>Yersinia pestis</i> F1-V gene and display the <i>Y. pestis</i> F1-V protein and dendritic cell-specific mAbs against lymphocyte antigen 75 (LY75; DEC205) led to antibody and interferon-γ (IFNγ; IFNγ) production, whereas injecting the analogous construct lacking the F1-V gene led to antibody production alone. Next steps include using the bacteriophage T4 heads to engineer vaccines for other infectious diseases.</p> <p>SciBX 6(14); doi:10.1038/scibx.2013.351 Published online April 11, 2013</p>	Patent application filed; unlicensed	<p>Tao, P. <i>et al. Proc. Natl. Acad. Sci. USA</i>; published online March 25, 2013; doi:10.1073/pnas.1300867110 Contact: Venigalla B. Rao, The Catholic University of America, Washington, D.C. e-mail: rao@cua.edu</p>
Cross-reactive anti-HIV antibody to guide vaccine epitope development	<p>Structural and evolutionary analysis of a new cross-reactive HIV antibody could be used to design vaccines to help prevent the disease. A time-course analysis of blood samples taken from a newly infected patient with HIV tracked the evolution of a new cross-reactive anti-HIV Env antibody that neutralized 55% of viral isolates <i>in vitro</i>. The antibody showed less somatic mutation than previously identified broadly neutralizing antibodies, and its germline B cell receptor precursor bound HIV Env with low nanomolar affinity. Next steps could include using HIV Env variants from this viral isolate to guide the design of vaccine epitopes.</p> <p>SciBX 6(14); doi:10.1038/scibx.2013.352 Published online April 11, 2013</p>	Patent applications filed; licensing status unavailable	<p>Liao, H.-X. <i>et al. Nature</i>; published online April 3, 2013; doi:10.1038/nature12053 Contact: Hua-Xin Liao, Duke University, Durham, N.C. e-mail: hliao@duke.edu Contact: Barton F. Haynes, same affiliation as above e-mail: barton.haynes@duke.edu</p>

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