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REThinking lung cancer

By Chris Cain, Staff Writer

Less than five years after the discovery of the EML4-ALK oncogenic fusion protein as a driver of non-small cell lung cancers, and less than a year after the FDA approved **Pfizer Inc.**'s Xalkori crizotinib to target that fusion in these tumors, four research teams have independently identified another tyrosine kinase fusion—KIF5B-RET oncogenic fusion protein—that could underlie about 2% of lung adenocarcinoma cases.¹⁻⁴ The findings provide a rationale for testing multi-tyrosine kinase inhibitors that target RET, including Sutent sunitinib, Caprelsa vandetanib and Nexavar sorafenib, in lung cancer and for developing more specific RET-targeted therapies.

One of the four groups, hailing from the **Dana-Farber Cancer Institute**, hopes to begin a Phase II trial of Pfizer's Sutent in KIF5B-RET-positive lung cancer patients in the first half of this year, and biotech **Xcovery Inc.** is now looking for more specific RET inhibitors based on the findings.

Adenocarcinoma is the most common form of lung cancer, accounting for about 40% of cases. Many oncogenic genetic alterations have been identified in this population, including the EML4-ALK fusion and activating mutations in *K-Ras* and *epidermal growth factor receptor (EGFR)*.

Identification of these alterations has led to the development of targeted therapies, the highest-profile example being Pfizer's Xalkori, a dual inhibitor of c-Met receptor tyrosine kinase (MET; c-Met; HGFR) and anaplastic lymphoma kinase (ALK), and their oncogenic variants. The drug was approved last August and is indicated for the 5% of patients with non-small cell lung cancer (NSCLC) who have EML4-ALK fusions.

However, a large fraction of adenocarcinoma patients do not carry any known oncogenic drivers. Thus, four research teams set out to identify additional genetic alterations that could inform the development of new targeted therapies for lung cancer. Each team independently came to the same conclusion: a genomic translocation that creates a fusion of *kinesin family member 5B (KIF5B)* and *ret proto-oncogene (RET)* drives about 2% of lung adenocarcinoma cases.

RET is a receptor tyrosine kinase whose excess activation drives cancer cell growth. Activating mutations or translocations involving RET have been linked to the development of thyroid cancer. RET had not been previously implicated in lung cancer, and KIF5B-RET fusions had never before been detected.

Two of the teams, one from **Seoul National University** and one from Japan's **National Cancer Center Research Institute**, found the



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Publisher: Peter Collins, Ph.D.

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KIF5B-RET fusion by performing whole-transcriptome sequencing in lung adenocarcinoma samples to identify new oncogenic gene fusions.^{1,2} Follow-up studies using RT-PCR and expression analysis confirmed the findings in a larger set of patient samples.

A group from the **Japanese Foundation for Cancer Research (JFCR)** and a team from Dana-Farber and **Foundation Medicine Inc.** found *KIF5B-RET* by taking a more targeted approach to identify genetic alterations.

The JFCR team had previously identified *KIF5B-ALK* fusions in lung cancer, and they suspected the *KIF5B* locus might be a hot spot for additional genomic translocations. Thus, the group used fluorescent *in situ* hybridization (FISH) to look for *KIF5B* fusions.³

The Dana-Farber–Foundation Medicine team applied the company’s targeted-sequencing approach, which involves high-coverage sequencing of specific cancer-associated introns and exons.⁴

On average, the four groups found *KIF5B-RET* in about 2% of lung adenocarcinoma patients. None of these patients harbored a previously known oncogenic driver.

To confirm the oncogenic potential of *KIF5B-RET*, three of the teams transformed the fusion into cultured cell lines and found it drove unchecked growth.

The next question was whether inhibiting *KIF5B-RET* had therapeutic potential. The three teams tested tyrosine kinase inhibitors (TKIs) with broad-spectrum activity including against RET: Caprelsa, Nexavar or Sutent.²⁻⁴ Indeed, treatment of *KIF5B-RET*-transformed cells with any one of the drugs inhibited growth compared with treatment using vehicle or kinase inhibitors that did not act on RET. All three compounds displayed about equivalent potency.⁴

Results from the Korean team were published in *Genome Research*, while results from the other three teams were published in *Nature Medicine*.

“These papers very nicely demonstrate the technological power we can now use to unravel genomic alterations, and [they] present a prototypical example of how smartly designed approaches can identify patients who will benefit from targeted therapy,” said Roman Thomas, coordinator of the Clinical Lung Cancer Genome Project, a large international lung cancer genomics consortium. “This work shows us that genomic strategies have fulfilled their promise.”

He noted that the genomic approaches used to identify *KIF5B-RET* are distinct from the functional screening approaches that led to the identification of *EML4-ALK* five years ago, and he thinks the new approaches will continue to lead to the identification of new cancer targets.

Thomas, who is also professor of translational genomics at the **University of Cologne**, was not involved in this work. In 2010 and 2011, he published papers that found amplification of *fibroblast growth factor*

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—Roman Thomas,
University of Cologne

receptor 1 (FGFR1; CD331) and mutation of *discoïdin domain receptor tyrosine kinase 2 (DDR2)* in squamous cell lung cancer, which could lead to new targeted therapies for the disease.⁵⁻⁸

Despite the different approaches, Chris Liang, CSO, EVP and director at Xcovery, said, “The RET story so far mimics the ALK story: both fusions are activating, patients with RET fusions do not have other genetic changes, and they tend to be nonsmokers. So it’s tempting to conclude that inhibiting RET in these patients can have therapeutic benefits, just like the ALK inhibitor Xalkori.”

Finding a new purpose

Pasi Jänne, associate professor of medicine at **Harvard Medical School** and Dana-Farber and colead author on the study, told *SciBX* that based on the results, he hopes to begin an investigator-initiated Phase II trial of Sutent in *KIF5B-RET*-positive lung cancer patients in “the next few months.”

“I think with the data in hand, and everything we know about oncogenic kinases and kinase inhibitors, a clinical trial is a next appropriate step,” said Jänne. “I don’t think there is a critical piece of data that we are missing that would deter the path moving forward to the clinic. We will of course continue to study the biology of *KIF5B-RET* both *in vitro* and *in vivo*.”

Although *KIF5B-RET* occurred in fewer patents than the *EML4-ALK* fusion, Jänne said the new findings are still important. “Lung cancer is such a common cancer that this translates into significant numbers of actual patients,” he said. “With an assumption of 2%, this would translate into about 4,000 new patients diagnosed annually.”

Sutent is marketed to treat gastrointestinal stromal tumors and advanced renal cell carcinoma. **AstraZeneca plc** markets Caprelsa to treat medullary thyroid cancer. Nexavar sorafenib is marketed by **Bayer AG** and **Onyx Pharmaceuticals Inc.** for liver and renal cancers.

AstraZeneca declined to comment, and Pfizer was unavailable for comment. Onyx told *SciBX* that the Phase III MISSION (Monotherapy administration of Sorafenib in patients with non-small cell lung cancer) trial of Nexavar in NSCLC is scheduled to read out in the first half of this year, and an analysis of undisclosed biomarkers is planned for patients who elected to provide tissue samples.

“A caveat is that the reported *in vitro* studies employed engineered cell lines instead of patient-derived cell lines, so it is critical to clinically validate the target,” said Liang.

Blueprint Medicines CSO Christoph Lengauer added that analysis of competitive kinase-binding data from the company’s in-house reference database suggests the three compounds differ in how potently they inhibit RET relative to their other known clinically relevant targets. He told *SciBX* these differences may affect their clinical utility in these patients.

He said RET was the 4th, 5th and 15th most potently inhibited kinase by Caprelsa, Sorafenib and Sutent, respectively. “Given the nonselective nature

of Sutent, our hypothesis is that it won’t work well and that there won’t be a suitable therapeutic window in patients,” he said. “Caprelsa is clinically active and approved in an indication where RET is likely a relevant target, and therefore may show activity in other RET-dependent indications.”

Jänne said that regardless of *in vitro* measurements, “at the end of the day you have to do the human experiment, which is the clinical trial.” He pointed to Xalkori as an example of a drug that is not an ideal inhibitor for its ALK target but still has clear clinical benefit.

One idea to provide additional insight into the clinical effectiveness of the compounds is to analyze ongoing or prior clinical trials of the TKIs in patients with lung cancer and determine whether the *KIF5B-RET* fusion is correlated with clinical response. Caprelsa, Nexavar and Sutent have all been tested in NSCLC because of their broad-spectrum TKI activity.

“In all of the studies the tumor response rate to each of these agents

is about 10%. It would be worthwhile going back to those patient specimens to see if they contain *RET* rearrangements,” said Jänne. “Unfortunately, the problem with many clinical trials is that they do not mandate tissue collection, and so the likelihood of such specimens being available to test is low.”

Liang agreed that clinical testing of existing TKIs should begin immediately but also said there is a strong rationale to develop more specific RET inhibitors. “The available RET inhibitors have such broad-spectrum inhibitory activity that they are associated with severe toxicities at their maximum tolerated dose,” he said. “More specific RET inhibitors should be better tolerated.”

“We are looking into the RET activity of our compounds because of these papers,” said Liang. “Our focus is to develop less-toxic compounds than the first-generation inhibitors, such as Nexavar, Sutent and

Caprelsa, so that they can be more suitable for combination with other therapies.”

Lengauer agreed that these findings could encourage the development of more specific RET inhibitors. “Before this work, the rationale for using drugs with RET-inhibitory activities in cancer patients was primarily based on the fact that many thyroid cancers carry mutations or translocations in RET. It likely hasn’t made much sense to develop specific RET inhibitors because the number of thyroid cancer patients with RET mutations who would benefit from targeted therapy was not well understood.”

He added that “because most kinase inhibitors are unselective, lots of compounds happen to hit RET, but as far as we know no one has made a truly specific RET inhibitor.”

Blueprint is developing selective kinase inhibitors targeting cancers driven by genomic alterations, but the company would not comment on its pipeline.

Detection connection

All four teams said clinical validation will go hand-in-hand with the development of diagnostics to identify patients who could respond to

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—**Christoph Lengauer,**
Blueprint Medicines

treatment with RET inhibitors.

Maureen Cronin, SVP of R&D at Foundation Medicine, said the company's test is well positioned to serve that purpose. The company's sequencing test examines thousands of specific exons and introns across about 200 genes associated with cancer, including *RET*, at an average of more than 200-fold coverage, which Cronin said gives the test higher sensitivity and specificity than whole-transcriptome sequencing.

The company, which started collaborating with Jänne after identifying *KIF5B-RET* in patients with lung adenocarcinoma, has additional undisclosed collaborations looking at genomic alterations in other cancer types.

"We think, based on what we have seen so far, *RET* rearrangements may be found more widely in cancer outside of lung adenocarcinoma. Because of the way our test is constructed, we will be able to find all rearrangements involving *RET*, whereas FISH analysis could only identify specific known rearrangements," said Cronin.

The list price of the test is \$5,800, and it is performed in a CLIA lab.

In addition to Foundation Medicine, both Japanese teams are pursuing the development of undisclosed diagnostics. The Korean researchers are developing a FISH assay to detect *KIF5B-RET* fusions.

Foundation Medicine has filed patents covering the detection of the fusion. The National Cancer Center Research Institute also has filed for a patent covering fusion detection and is in negotiations to license it to an undisclosed diagnostic company. **Macrogen Inc.**, which collaborated with the Korean team, has also filed for a patent and said the IP is available for licensing. JFCR did not disclose patent or licensing information.

Cain, C. *SciBX* 5(9); doi:10.1038/scibx.2012.219

Published online March 1, 2012

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Personalized medicine triumvirate

By Michael J. Haas, Senior Writer

Three Florida-based institutions are pooling resources in the Personalized Medicine Partnership of Florida, which is tasked with discovering markers that could predict individual responses to drugs for cancer, metabolic diseases and cardiovascular diseases.

PMP Florida combines preclinical research capabilities and technology platforms from the **Sanford-Burnham Medical Research Institute**, **Florida Hospital's** clinical research expertise and patient population, which is one of the largest in the state, and the **H. Lee Moffitt Cancer Center & Research Institute's** established protocols for obtaining and storing patient samples and data.

Sanford-Burnham and Florida Hospital already have a collaboration in personalized medicine. In 2008, they founded **The Translational Research Institute for Metabolism and Diabetes (TRI)** to identify preclinical and clinical markers that reflect subsets of heterogeneous metabolic and cardiovascular diseases.¹ PMP Florida will enable the two institutions to expand their efforts to include cancer and will add Moffitt's unique resources to their existing capabilities in personalized medicine research, Deborah Robison, director of communications at Sanford-Burnham, told *SciBX*.

Indeed, Moffitt was looking to apply its resources beyond cancer, said John Reed, CEO of Sanford-Burnham and professor at Sanford-Burnham's NCI-Designated Cancer Center.

Moffitt has "protocols for educating patients about participation in clinical trials and obtaining patients' consent to take DNA samples and gain access to their medical records and other data" that enables personalized medicine research, Reed said.

Additionally, "Moffitt has one of the world's largest biospecimen banks and robotic technology to aid sample storage and retrieval," he said.

Moffitt's protocols and technologies were developed for the center's Total Cancer Care program, which started in 2003 to aid the development and design of individualized cancer treatment regimens based on the genetic profile of a given tumor and the patient's lifestyle, medical history and other factors.

Exempli gratia

Although PMP Florida's steering committee has not yet selected specific projects, "we would like to conduct a number of small, focused pilot studies and then expand those to larger studies," said Reed.

As an example of a type of project PMP would pursue, Reed cited a study by a team from Sanford-Burnham and other academic institutions that sought to identify markers of response to β -blockers to treat heart failure in patients with diabetes.

Poor therapeutic response to those drugs is a major cause of relapse in patients with heart failure, "and re-admission to the hospital due to heart failure relapse is a problem that has a major healthcare cost," he said. "So the question was: could we find candidate genes that predict the risk of relapse and rehospitalization?"

The team focused on a SNP on *uncoupling protein 2 mitochondrial proton carrier (UCP2)* that is associated with increased risk of coronary artery disease (CAD) and diabetes. Because β -blockers decrease *UCP2* expression, the team hypothesized the presence or absence of the SNP could predict treatment responses in diabetic patients who received β -blockers following a diagnosis of myocardial infarction (MI) or unstable angina.

Indeed, in patients with diabetes who harbored the *UCP2* SNP, compared with patients who did not have diabetes, β -blocker therapy was associated with an 11-fold increase in the rate of rehospitalization due to cardiovascular issues. In patients with diabetes who did not have the SNP, β -blocker therapy resulted in an 80% decrease in the rate of rehospitalization compared with no β -blocker therapy.²

"So, one idea for PMP Florida is to expand this to a larger validation study to predict treatment outcomes and, ultimately, decrease healthcare costs" in this population of patients, Reed said.

This summer, the partners plan to identify a handful of pilot projects for PMP Florida from the research portfolio of each institution. Reed said the partnership expects to begin with two or three projects in cancer

and two or three in metabolic and cardiovascular diseases. Cancer projects would probably focus on response to targeted therapies, he added.

Robison said each partner will fund its own activities within PMP Florida and that the partners will share any IP generated by PMP Florida.

Additionally, "the partnership will be a vehicle to attract revenue," she said. "We will pursue collaborative grant opportunities at the state and federal levels, and we hope to attract the interest of biotech and pharma." Robison noted that PMP Florida has not yet determined when to apply for grants or at what stage to seek corporate partners for a given project.

She added that the respective projects of PMP Florida and TRI will be complementary rather than overlapping.

Haas, M.J. *SciBX* 5(9); doi:10.1038/scibx.2012.220
Published online March 1, 2012

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COMPANIES AND INSTITUTIONS MENTIONED

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Sanford-Burnham Medical Research Institute, La Jolla, Calif.
The Translational Research Institute for Metabolism and Diabetes, Orlando, Fla.

APOE in AD

By *Tim Fulmer, Senior Writer*

U.S. researchers have shown that **Eisai Co. Ltd.**'s cancer drug Targretin bexarotene raises apolipoprotein E levels in the brain and partially reverses cognitive and behavioral deficits in a mouse model of Alzheimer's disease.¹ Based on the findings, the team founded **ReXceptor Inc.**, which plans to begin a proof-of-concept AD trial in about two months.

Apolipoprotein E (APOE) occurs in three isoforms—APOE2, APOE3 and APOE4—that serve as lipid-carrying proteins in the serum and brain.

Prior work by ReXceptor founder Gary Landreth, a professor of neuroscience at the **Case Western Reserve University School of Medicine**, and others showed that raising APOE levels led to downstream clearance of β -amyloid ($A\beta$) in mouse models of AD.^{2,3} The challenge was figuring out the best way to increase those levels.

To do that, Landreth and colleagues decided to focus on activating the three nuclear receptors that upregulate APOE expression: peroxisome proliferation-activated receptor- γ (PPARG; PPAR γ), liver X receptor (LXR) and retinoid X receptor (RXR).

In earlier work, Landreth's team had shown that an LXR agonist enhanced APOE levels in the brain, which in turn increased both $A\beta$ degradation and cognition in mice.⁴ The study provided proof of concept that agonizing the nuclear receptors could lead to improvements in AD, but the researchers did not pursue the LXR angle because agonists of that target have a poor side-effect profile.

Landreth was further dissuaded from targeting PPAR γ , at least partly, because of data from a Phase III trial in AD disclosed by **GlaxoSmithKline plc** in 2009, in which GSK's PPAR γ agonist Avandia rosiglitazone failed to increase cognition and memory compared with placebo. GSK markets the drug to treat type 2 diabetes.

Thus, Landreth focused on activating RXR, which is the target of at least one approved drug: Targretin to treat cutaneous T cell lymphoma (CTCL). Targretin was developed by **Ligand Pharmaceuticals Inc.**, which sold the drug, along with the rest of its cancer portfolio, to Eisai in 2006.

Eisai did not return calls or e-mails requesting comment.

In cultured microglia and astrocytes, Targretin stimulated expression of APOE, promoted degradation of soluble $A\beta$ and increased secretion of high-density lipoprotein (HDL) particles compared with no treatment.

In a mouse model of AD, Targretin led to greater APOE expression, increased HDL, a 30% decrease in soluble $A\beta$ and a 75% decrease in $A\beta$ plaques in the hippocampus and cortex compared with vehicle. The lower $A\beta$ levels were associated with behavioral and cognitive improvements in the mice.

Analysis of brain tissue showed that Targretin-treated mice also had more $A\beta$ -laden microglia, suggesting that Targretin lowered $A\beta$ levels by a dual mechanism: increasing both APOE levels and the phagocytic activity of microglia.

"Thus, activation of RXR by Targretin stimulates two distinct cellular

processes—increased APOE/HDL levels as well as enhanced microglial activation—both of which are disease modifying," said Landreth.

Prior work by other labs has shown that activated microglia can migrate to $A\beta$ depositions and clear them from the brain via phagocytosis.⁵⁻⁷

The new findings were published in *Science*.

Finding the right model

Robert Mahley, president emeritus of **The J. David Gladstone Institutes** and founder of **ApoBiopharma Inc.**, told *SciBX* the mouse model used in the paper is poorly predictive of success in the clinic. "Mouse ApoE does not behave structurally or functionally like human APOE3 and APOE4. Moreover, this is an exaggerated mouse model of excess production of the amyloid precursor protein and $A\beta$," he said. "We cannot draw conclusions about a response in humans from the design of this study."

A more predictive mouse model would express the human APOE isoforms. Indeed, David Holtzman wanted to see "if the same *Science* findings are replicated in the presence of human APOE isoforms" in APOE knock-in mice.

In 2011, Holtzman and colleagues published in *The Journal of Neuroscience* that such mice have varying levels of $A\beta$ plaque burden depending on the number of copies of *APOE3* and *APOE4* genes.⁸

Holtzman is professor of neurology and developmental biology and associate director of the Alzheimer's Disease Research Center at **Washington University in St. Louis**.

Landreth said he and Holtzman are discussing a collaboration to study the mechanism of RXR activation in the APOE knock-in mice.

Divided we stand

Despite sharing the common goal of targeting APOE to lower downstream levels of toxic $A\beta$, the approaches of ReXceptor and ApoBiopharma are separated by "a wide philosophical divide," said Landreth (*see Figure 1, "Two theories on APOE in AD"*).

ReXceptor is trying to increase extracellular levels of all APOE isoforms, whereas ApoBiopharma wants to decrease intracellular levels of a single isoform—APOE4. That isoform is converted into cytotoxic fragments by intracellular proteases. The differing strategies reflect uncertainty about the exact mechanism of action of APOE in AD.

"I believe, based on our work, that any benefit of removing amyloid by increasing APOE levels will be significantly offset by increased production of the APOE4 isoform, which is a neurotoxic protein," said Mahley. "Our approach is to attack the detrimental effects of APOE4."

ApoBiopharma is taking a two-pronged approach to lowering APOE4 levels.

One strategy is to identify small molecules that bind APOE4 and convert it into a nontoxic form that resembles APOE3. In 2011, Mahley and colleagues published the identification of small molecule 'structure correctors' of APOE4 that decreased the protein's neurotoxic effects in cultured neurons.⁹

"Thus, activation of RXR by Targretin stimulates two distinct cellular processes—increased APOE/HDL levels as well as enhanced microglial activation—both of which are disease modifying."

**—Gary Landreth,
Case Western Reserve University
School of Medicine**

Figure 1. Two theories on APOE in AD.

Two biotechs are targeting apolipoprotein E (APOE) isoforms in the brain to lower levels of toxic β -amyloid ($A\beta$) and treat Alzheimer's disease (AD). Their approaches differ and are guided by two divergent hypotheses of how APOE contributes to disease.

APOE occurs in three different isoforms—APOE2, APOE3 and APOE4—which carry lipids between various cells in the brain. Genetic studies have linked APOE4 to increased risk of late-onset AD compared with APOE2 or APOE3. However, the precise mechanistic roles the three isoforms play in AD pathophysiology is unclear.

In a paper in *Science*, **ReXceptor Inc.** founder Gary Landreth and colleagues at the **Case Western Reserve University School of Medicine** showed that the retinoid X receptor (RXR) agonist Targretin bexarotene upregulated all APOE isoforms, [a(1)] which blocked $A\beta$ aggregates [b] and decreased AD-associated behavioral and cognitive deficits in mice [c].

Targretin is marketed by **Eisai Co. Ltd.** to treat cutaneous T cell lymphoma (CTCL). ReXceptor is developing its own formulations of RXR agonists based on Targretin.

An alternative theory proposed by **ApoBiopharma Inc.** founder Robert Mahley of **The J. David Gladstone Institutes** postulates that the APOE4 isoform is intrinsically toxic to neurons compared with the other isoforms. The toxicity derives from the cleavage products of APOE4 when it is degraded by cellular proteases [a(2)]. Therefore, the company's goal is to treat disease by selectively lowering APOE4 levels and decreasing downstream toxicity that leads to sick and dying neurons [b and c].

In 2011, Mahley and colleagues published in *The Journal of Biological Chemistry* that small molecule 'structure correctors', which convert the toxic structure of APOE4 into less toxic forms, showed lower toxicity in cultured wild-type mouse neurons than no treatment.

Mahley and the **University of California, San Francisco** have licensed the structure correctors to ApoBiopharma.

The second approach is to identify small molecule inhibitors of the proteases that convert APOE4 into toxic fragments.

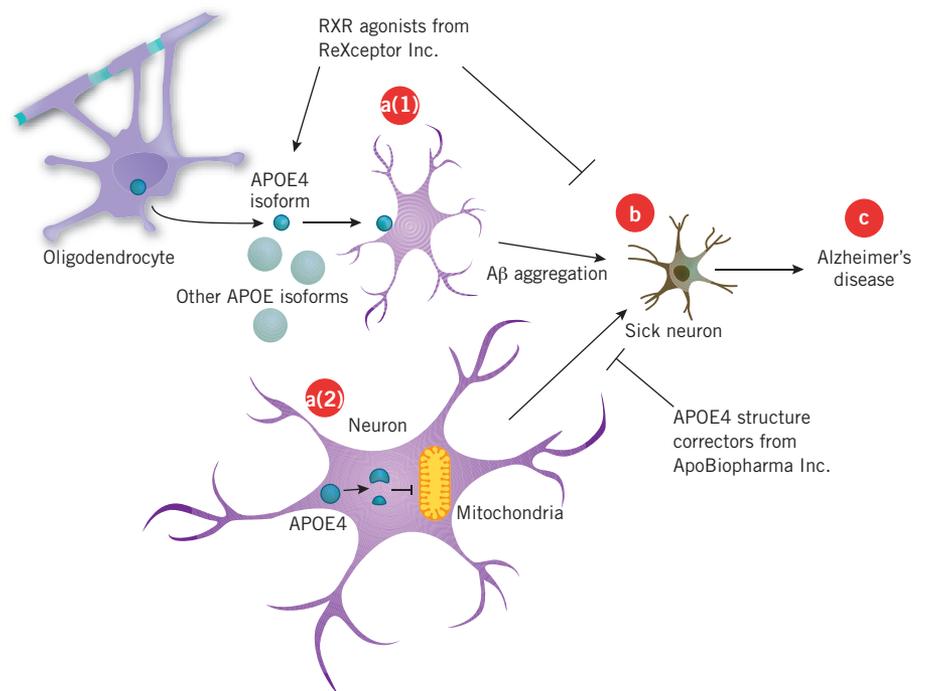
"We are currently performing *in vivo* mouse studies to demonstrate that the structure correctors can correct learning and memory problems that exist in mice expressing APOE4. This will provide evidence that our approach could be useful in humans," said Mahley.

Landreth said ReXceptor plans to start a small pilot trial of Targretin in a couple of months. "This will be a proof-of-concept trial in 12 healthy volunteers—6 receiving Targretin, 6 placebo—in which we monitor CSF [cerebrospinal fluid] levels of $A\beta$ and APOE over a period of 4 months," he said. "Those data should give us an initial idea of the activity of Targretin in patients and whether there are any potential safety issues."

Based on the results, ReXceptor hopes to determine a formulation and dosing regimen of Targretin to treat AD, said Landreth. He added that IP based around that formulation should help ReXceptor compete with generic forms of the drug, which goes off patent in April.

The *Science* findings are covered by patents that are exclusively licensed to ReXceptor from Case Western.

Fulmer, T. *SciBX* 5(9); doi:10.1038/scibx.2012.221
Published online March 1, 2012

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COMPANIES AND INSTITUTIONS MENTIONED

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Case Western Reserve University School of Medicine, Cleveland, Ohio
Eisai Co. Ltd. (Tokyo:4523; Osaka:4523), Tokyo, Japan
GlaxoSmithKline plc (LSE:GSK; NYSE:GSK), London, U.K.
The J. David Gladstone Institutes, San Francisco, Calif.
Ligand Pharmaceuticals Inc. (NASDAQ:LGND), La Jolla, Calif.
ReXceptor Inc., Cleveland, Ohio
University of California, San Francisco, Calif.
Washington University in St. Louis, St. Louis, Mo.

DNA nanorobots

By Lauren Martz, Staff Writer

Researchers at the **Wyss Institute for Biologically Inspired Engineering at Harvard University** have designed drug delivery vehicles dubbed DNA nanorobots that allow for complex targeting and controlled drug release.¹ Although targeted delivery is hardly a new concept, the DNA nanorobots go one step beyond existing approaches by enabling conditional payload release based on the presence of combinations of markers on target cells, thus making delivery more specific and controlled.

The Wyss team's technology has the potential to improve the safety and efficacy of a variety of therapeutics, but several steps, including design changes to increase time in circulation and decrease immunogenicity, could be required before progressing to clinical trials.

Previous studies have shown that DNA constructs can be designed to perform robotic functions including computing and sensing.² Building on those studies, a Wyss team led by George Church used a computer-aided 'DNA origami' method, which folds single-stranded DNA into a customized shape, to design the nanorobot delivery system.

The nanorobots were designed with a two-part DNA barrel shape capable of holding 12 payload molecules inside. The two parts are held together by customized oligonucleotide aptamers that induce a conformational change upon binding specific peptide targets, which opens the barrel and exposes the payload.

Church is a founding core faculty member at the Wyss Institute, professor of genetics at **Harvard Medical School** and professor of health sciences at **Harvard University** and the **Massachusetts Institute of Technology**.

As proof of concept, the team loaded nanorobots with fluorescently labeled antibody fragments against human leukocyte antigen (HLA) and designed aptamers that specifically bound surface peptides found on cancer cells. Each nanorobot was held together by two aptamers designed to bind the same or different peptide targets. Nanorobots targeting two distinct cell surface peptides allowed better cell selectivity. The nanorobots exposed payload, as indicated by increased fluorescence signal, only when cultured in cell types expressing the target surface peptide or peptides.

To show that the nanorobots could bind to specific cell types, the team mixed large granular lymphocytic leukemia cells with a Burkitt's lymphoma cell line or whole-blood leukocytes and added a nanorobot with DNA aptamers that recognized a protein only found on the leukemia cells. In both cultures, the nanorobots specifically detected the leukemia cells.

The next step was determining the sensitivity of the nanorobots. The team developed a culture of mixed lymphoma and leukemia cells with varying concentrations of each cell type. Nanorobots designed to target the leukemia cells were able to detect them at concentrations as low as the single-cell level.

Finally, the team tested the therapeutic potential of the structures *in vitro*. Nanorobots loaded with antibodies against the known cancer targets CD33 and sialic acid binding Ig-like lectin 7 (SIGLEC7; CDw328) and with aptamer locks targeting a leukemia surface protein produced dose-dependent arrest of leukemia cell growth.

“The idea is to develop the capability for controlled delivery or release of payloads in response to cell surface markers that may be present on one cell population while not responding to nontarget cells that do not bear the same combination or markers.”

—Shawn Douglas, Harvard University

The work was published in *Science*.

Rather than just steady release over time of a drug that can bind target and nontarget cells alike, Church noted that the nanorobot technology has programmable logic in a very tiny package—smaller than a cell.

“The idea is to develop the capability for controlled delivery or release of payloads in response to cell surface markers that may be present on one cell population while not responding to nontarget cells that do not bear the same combination of markers,” added Shawn Douglas, technology development fellow at the Wyss institute and co-corresponding author on the paper.

“We can finally integrate sensing and logical computing functions via complex yet predictable nanostructures, which are some of the first hybrids of structural DNA, antibodies, aptamers and metal atomic clusters,” added Douglas.

Nanorobot redesign

Church said the team's nanorobots could be applied to “any therapeutic or diagnostic that could benefit from sensing, logic, actuation and targeted delivery.” The indications his team are studying include cancer, immune modulation and autoimmunity.

Douglas told *SciBX*, “The first step is to scale up production of our devices so we have enough material to work in an animal model. We need about 1,000 times more material for these

experiments than we did for the current study.”

Church added that his team is “moving on to rodent efficacy and toxicity testing—then cost reduction protocols and clinical trials.”

According to Douglas, the team hopes to publish follow-up studies showing function in animals in the next two years.

Both Church and Douglas said the nanorobots likely will need design alterations before the product is ready for the clinic.

“It is possible that the DNA sequence we used is immunogenic due to unmethylated CpG sites,” noted Douglas. “We might address this by redesigning the sequence to not include those bases.”

Additionally, he told *SciBX* that the team will probably need to redesign the nanorobot so that it can stably circulate in the bloodstream long enough for it to find its protein target and release its payload.

Harvard University has filed a patent application for the nanorobots, and the technology is available for licensing.

Martz, L. *SciBX* 5(9); doi:10.1038/scibx.2012.222

Published online March 1, 2012

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Contact: Shawn M. Douglas, Harvard Medical School, Boston, Mass.
e-mail: shawn.douglas@wyss.harvard.edu
Contact: George M. Church, same affiliation as above
e-mail: gmc@harvard.edu
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COMPANIES AND INSTITUTIONS MENTIONED

Harvard Medical School, Boston, Mass.
Harvard University, Cambridge, Mass.
Massachusetts Institute of Technology, Cambridge, Mass.
Wyss Institute for Biologically Inspired Engineering at Harvard University, Cambridge, Mass.

This week in therapeutics

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

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

Indication	Target/marker/pathway	Summary	Licensing status	Publication and contact information
Autoimmune disease				
Autoimmune disease	IL-5	Rat studies suggest IL-5 could help treat autoimmune diseases. In a rat model of experimental autoimmune neuritis, daily injection with recombinant IL-5 increased the number of autoantigen-specific T _{reg} cells in nerves and decreased disease severity and weight loss compared with control injection. Next steps could include developing compounds that increase IL-5 signaling and evaluating them in models of autoimmune disease. SciBX 5(9); doi:10.1038/scibx.2012.223 Published online March 1, 2012	Patent application filed; licensing status unavailable	Tran, G.T. <i>et al. Blood</i> ; published online Feb. 6, 2012; doi:10.1182/blood-2011-12-396101 Contact: Suzanne J. Hodgkinson, The University of New South Wales, Sydney, New South Wales, Australia e-mail: s.hodgkinson@unsw.edu.au
Rheumatoid arthritis (RA)	Receptor tyrosine kinase-like orphan receptor 2 (ROR2); wingless-type MMTV integration site family member 5A (WNT5A)	Mouse studies suggest inhibiting WNT5A-ROR2 signaling could help treat RA and RA-associated bone erosion. In mice, a deficiency of Wnt ligand <i>Wnt5a</i> or its receptor <i>Ror2</i> decreased the formation of bone-resorbing osteoclasts compared with no deficiency. In two mouse models of RA, a <i>Ror2</i> fusion protein that acts as a <i>Wnt5a</i> decoy receptor lowered inflammation and bone erosion compared with a control protein. Next steps could include testing the fusion protein in animal models of other bone diseases. SciBX 5(9); doi:10.1038/scibx.2012.224 Published online March 1, 2012	Patent and licensing status unavailable	Maeda, K. <i>et al. Nat. Med.</i> ; published online Feb. 19, 2012; doi:10.1038/nm.2653 Contact: Naoyuki Takahashi, Matsumoto Dental University, Nagano, Japan e-mail: takahashinao@po.mdu.ac.jp Contact: Yasuhiro Kobayashi, same affiliation as above e-mail: ykoba@po.mdu.ac.jp
Cancer				
Brain cancer	Sulfatase 2 (SULF2)	Human tissue and mouse studies suggest antagonizing SULF2 could help treat glioblastoma multiforme (GBM). In a panel of GBM tumor samples and tumor cell lines, about 50% of tumors had higher SULF2 expression than healthy controls. In a mouse model of GBM, tumor cells lacking <i>Sulf2</i> had lower growth rates and were less lethal than wild-type tumor cells. Next steps include identifying small molecule or mAb antagonists of SULF2 and testing them in mouse models of GBM. SciBX 5(9); doi:10.1038/scibx.2012.225 Published online March 1, 2012	Unpatented; licensing status not applicable	Phillips, J.J. <i>et al. J. Clin. Invest.</i> ; published online Feb. 1, 2012; doi:10.1172/JCI58215 Contact: Joanna J. Phillips, University of California, San Francisco, Calif. e-mail: joanna.phillips@ucsf.edu Contact: Zena Werb, same affiliation as above e-mail: zena.werb@ucsf.edu
Colon cancer	MAP kinase kinase kinase 7 (MAP3K7; TAK1); K-Ras	Cell culture and mouse studies suggest inhibiting TAK1 could help treat K-Ras-dependent colon cancers. In K-Ras-mutant colon cancer cell lines in which K-Ras depletion leads to apoptosis, TAK1 expression was greater than that in K-Ras-mutant cell lines insensitive to K-Ras depletion. In mouse xenograft models of K-Ras-dependent colon cancer, a small molecule TAK1 inhibitor decreased tumor growth compared with vehicle. Next steps could include testing TAK1 inhibitors in additional preclinical models of K-Ras-dependent colon cancers. SciBX 5(9); doi:10.1038/scibx.2012.226 Published online March 1, 2012	Patent and licensing status undisclosed	Singh, A. <i>et al. Cell</i> ; published online Feb. 17, 2012; doi:10.1016/j.cell.2011.12.033 Contact: Daniel A. Haber, Massachusetts General Hospital Cancer Center, Charlestown, Mass. e-mail: haber@helix.mgh.harvard.edu Contact: Jeff Settleman, same affiliation as above e-mail: settleman.jeffrey@gene.com

This week in therapeutics (continued)

Indication	Target/marker/ pathway	Summary	Licensing status	Publication and contact information
Endocrine/metabolic disease				
Hypercholesterolemia	Proprotein convertase subtilisin/kexin type 9 (PCSK9)	<p>Mouse and nonhuman primate studies suggest an anti-PCSK9 antibody with pH-sensitive binding could treat hypercholesterolemia more effectively than non-pH-sensitive anti-PCSK9 antibodies. Anti-PCSK9 antibodies can be degraded if bound to their target at low pH. In mice and nonhuman primates, an anti-PCSK9 antibody with pH-sensitive binding had greater serum half-life and duration of cholesterol-lowering effect than a non-pH-sensitive anti-PCSK9 antibody. Next steps could include testing pH-sensitive anti-PCSK9 antibodies in clinical trials. PF-04950615, a humanized PCSK9 antibody from Pfizer Inc., is in Phase II testing to treat hypercholesterolemia. Pfizer has not disclosed whether the antibody has pH-sensitive binding. At least six other companies have PCSK9 inhibitors in Phase II testing or earlier to treat hypercholesterolemia and cardiovascular diseases.</p> <p>SciBX 5(9); doi:10.1038/scibx.2012.227 Published online March 1, 2012</p>	Patent and licensing status unavailable	<p>Chaparro-Riggers, J. <i>et al. J. Biol. Chem.</i>; published online Jan. 31, 2012; doi:10.1074/jbc.M111.319764</p> <p>Contact: Javier Chaparro-Riggers, Rinat-Pfizer Inc., South San Francisco, Calif. e-mail: javier.chaparro-riggers@rinat.pfizer.com</p>
Infectious disease				
Leishmaniasis	Not applicable	<p>Cell culture and mouse studies suggest the nitroimidazole compound fexinidazole could help treat leishmaniasis. In a mouse model of <i>Leishmania donovani</i> infection, fexinidazole inhibited parasite growth and increased survival compared with vehicle. Next steps include testing the compound in preclinical models of chronic infection with geographically diverse and drug-resistant <i>Leishmania</i> isolates.</p> <p>Sanofi and the Drugs for Neglected Diseases initiative have fexinidazole in Phase I testing for African trypanosomiasis.</p> <p>SciBX 5(9); doi:10.1038/scibx.2012.228 Published online March 1, 2012</p>	Unpatented; licensing status not applicable	<p>Wyllie, S. <i>et al. Sci. Transl. Med.</i>; published online Feb. 1, 2012; doi:10.1126/scitranslmed.3003326</p> <p>Contact: Alan H. Fairlamb, University of Dundee, Dundee, U.K. e-mail: a.h.fairlamb@dundee.ac.uk</p>
Respiratory syncytial virus (RSV)	RSV F protein	<p><i>In vitro</i> studies suggest antibodies targeting the prefusion conformation of the RSV F protein could be a more efficient alternative to current RSV prophylactics. Current RSV prophylactics target both the prefusion and postfusion conformations of RSV F protein. Preparations of human RSV F immunoglobulin without antibodies against the postfusion conformation retained most of their original neutralizing activity. Next steps include preparing neutralizing mAbs specific for the prefusion RSV F protein conformation and comparing them with Synagis palivizumab.</p> <p>AstraZeneca plc and Abbott Laboratories market the humanized anti-RSV F mAb Synagis as a prophylactic for RSV.</p> <p>AstraZeneca's motavizumab (MEDI-524), a humanized anti-RSV F mAb, is in Phase II trials as a prophylactic for RSV.</p> <p>SciBX 5(9); doi:10.1038/scibx.2012.229 Published online March 1, 2012</p>	Prefusion antibodies patented; available for licensing	<p>Magro, M. <i>et al. Proc. Natl. Acad. Sci. USA</i>; published online Feb. 8, 2012; doi:10.1073/pnas.1115941109</p> <p>Contact: José A. Melero, National Center for Microbiology and the Center of Biomedical Investigation Network for Respiratory Disease, Madrid, Spain e-mail: jmelero@isciii.es</p>

This week in therapeutics (continued)

Indication	Target/marker/pathway	Summary	Licensing status	Publication and contact information
Inflammation				
Inflammation	Crystallin α B (CRYAB; HSPB5)	<i>In vitro</i> studies identified a mechanism for HSPB5's anti-inflammatory activity that could help improve treatment of multiple sclerosis (MS). HspB5 is known to relieve symptoms in mouse models of MS. In plasma samples from six patients with MS, immunoprecipitation studies identified about 70 proinflammatory proteins that bound to HSPB5. The binding of such proteins to HSPB5 increased with rising temperature, suggesting that temperature-mediated binding to these proteins decreases inflammation. Next steps could include toxicity testing of HSPB5. SciBX 5(9); doi:10.1038/scibx.2012.230 Published online March 1, 2012	Use of HSPB5 for treating inflammatory disorders is patented; exclusively licensed to Cardinal Therapeutics Inc.; available for licensing and partnerships	Rothbard, J.B. <i>et al. J. Biol. Chem.</i> ; published online Feb. 3, 2012; doi:10.1074/jbc.M111.337691 Contact: Lawrence Steinman, Stanford University School of Medicine, Stanford, Calif. e-mail: steinman@stanford.edu
Inflammation	Lipin 2 (LPIN2)	Cell culture studies suggest increasing LPIN2 activity could help prevent fatty acid-induced inflammation, which has been linked to diseases including type 2 diabetes. In mouse and human macrophage cell lines exposed to fatty acids, small interfering RNA against <i>LPIN2</i> increased expression of proinflammatory genes compared with control siRNA. In the fatty acid-exposed mouse cell line, <i>Lpin2</i> overexpression decreased expression of proinflammatory genes compared with that seen using a control vector. Next steps include studying <i>Lpin2</i> -regulated inflammation in animal models. SciBX 5(9); doi:10.1038/scibx.2012.231 Published online March 1, 2012	Patent and licensing status undisclosed	Valdearcos, M. <i>et al. J. Biol. Chem.</i> ; published online Feb. 8, 2012; doi:10.1074/jbc.M112.342915 Contact: María A. Balboa, University of Valladolid School of Medicine, Valladolid, Spain e-mail: mbalboa@ibgm.uva.es
Musculoskeletal disease				
Muscular dystrophy	Dysferlin (DYSF); proteasome	Cell culture studies suggest inhibiting proteasome-mediated degradation of <i>DYSF</i> could help treat muscular dystrophy. In human myoblasts with missense mutations in the <i>DYSF</i> gene, the proteasome inhibitors Velcade bortezomib and lactacystin rescued the ability to repair membrane injuries and induce myotubule formation. Next steps include proof-of-concept studies evaluating Velcade in patients with missense mutations in <i>DYSF</i> . Takeda Pharmaceutical Co. Ltd. and Johnson & Johnson market Velcade to treat multiple myeloma (MM) and mantle cell lymphoma (MCL). Lactacystin is a bacteria-derived chemical reagent that inhibits the proteasome. SciBX 5(9); doi:10.1038/scibx.2012.232 Published online March 1, 2012	Unpatented; unavailable for licensing	Azaker, B.A. <i>et al. J. Biol. Chem.</i> ; published online Feb. 8, 2012; doi:10.1074/jbc.M111.329078 Contact: Michael Sinnreich, University Hospital Basel, Basel, Switzerland e-mail: msinnreich@uhbs.ch
Neurology				
Alzheimer's disease (AD)	Retinoid X receptor (RXR)	Mouse studies suggest agonizing RXR in the brain could help treat AD. In mouse models of AD, the oral small molecule RXR agonist Targretin bexarotene increased apolipoprotein E (APOE) expression, lowered hippocampal levels of soluble and insoluble toxic β -amyloid (A β) and decreased behavioral and cognitive deficits compared with vehicle control. ReXceptor Inc. will evaluate the safety of Targretin in a pilot trial in 12 healthy volunteers. Targretin is marketed by Eisai Co. Ltd. to treat cutaneous T cell lymphoma (CTCL; see APOE in AD, page 6). SciBX 5(9); doi:10.1038/scibx.2012.233 Published online March 1, 2012	Use of Targretin to treat AD patented by Case Western Reserve University; exclusively licensed to ReXceptor	Cramer, P.E. <i>et al. Science</i> ; published online Feb. 9, 2012; doi:10.1126/science.1217697 Contact: Gary E. Landreth, Case Western Reserve University School of Medicine, Cleveland, Ohio e-mail: gel2@case.edu

This week in therapeutics (continued)

Indication	Target/marker/pathway	Summary	Licensing status	Publication and contact information
Stroke	Discs large homolog 4 (DLG4; PSD95)	<p>Mouse studies identified a peptide-based PSD95 inhibitor that could help treat stroke. PSD95 inhibitors containing two distinct PSD95-binding peptides and a cell-penetrating peptide to increase blood brain barrier penetration were synthesized. In a mouse model of cerebral ischemia, injection of the inhibitors after insult decreased infarct size and restored motor performance compared with saline injection. Next steps include testing the inhibitors in additional ischemic models and in animal models of pain.</p> <p><i>SciBX</i> 5(9); doi:10.1038/scibx.2012.234 Published online March 1, 2012</p>	Patent applications filed; available for licensing	<p>Bach, A. <i>et al. Proc. Natl. Acad. Sci. USA</i>; published online Feb. 17, 2012; doi:10.1073/pnas.1113761109 Contact: Kristian Strømgaard, University of Copenhagen, Copenhagen, Denmark e-mail: krst@farma.ku.dk Contact: Anders Bach, same affiliation as above e-mail: anba@farma.ku.dk</p>

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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			
RNA sequencing of multiple drug-resistant cells to identify therapeutic targets and mechanisms of action	<p><i>In vitro</i> studies suggest RNA sequencing of drug-resistant cells could help identify a compound's therapeutic target. As proof of concept, RNA sequencing of human colon cancer cell lines resistant to BI2536 confirmed polo-like kinase 1 (PLK1; STPK13) as the compound's molecular target. For validation, the method also was used to show that the $\beta 5$ subunit of the proteasome (PSMB5; LMPX) is the molecular target of Velcade bortezomib, which is a known proteasome inhibitor. The method was less effective at identifying molecular targets for compounds with multiple targets. Next steps include applying the technology to a larger panel of compounds. Takeda Pharmaceutical Co. Ltd. markets Velcade to treat mantle cell lymphoma (MCL) and multiple myeloma (MM). At least three companies have PLK1 inhibitors in clinical and preclinical testing to treat cancers.</p> <p>SciBX 5(9); doi:10.1038/scibx.2012.235 Published online March 1, 2012</p>	Patent application filed covering the method; available for licensing	<p>Wacker, S.A. <i>et al. Nat. Chem. Biol.</i>; published online Feb. 12, 2012; doi:10.1038/nchembio.779 Contact: Tarun M. Kapoor, The Rockefeller University, New York, N.Y. e-mail: kapoor@rockefeller.edu Contact: Olivier Elemento, Weill Cornell Medical College, New York, N.Y. e-mail: ole2001@med.cornell.edu</p>
Disease models			
Cellular model for Alzheimer's disease (AD) based on induced pluripotent stem (iPS) cells and embryonic stem cells (ESCs) from patients with Down syndrome	<p>A cellular model for AD in Down syndrome could help identify mechanisms of AD and test AD therapeutics. Individuals with Down syndrome have a high incidence of early onset AD. Cortical neurons derived from iPS cells or ESCs from patients with Down syndrome had key pathological features of AD, including increased levels of both pathogenic β-amyloid ($A\beta$) and phosphorylated microtubule-associated protein-τ (MAPT; TAU; FTDP-17), whereas stem cell-derived neurons from healthy controls did not. In the Down syndrome-derived neurons, a γ-secretase inhibitor prevented $A\beta$ peptide production. Next steps could include testing AD therapeutics in the model.</p> <p>SciBX 5(9); doi:10.1038/scibx.2012.236 Published online March 1, 2012</p>	Patent and licensing status unavailable	<p>Shi, Y. <i>et al. Sci. Transl. Med.</i>; published online Feb. 15, 2012; doi:10.1126/scitranslmed.3003771 Contact: Frederick J. Livesey, University of Cambridge, Cambridge, U.K. e-mail: rick@gurdon.cam.ac.uk</p>
Inducible mouse model of ovarian cancer	<p>Mice with inducible ablation of p53 and activation of K-Ras in the ovary and/or oviduct could aid the development of new treatments for ovarian cancer. In immunocompetent adult mice, inducible p53 ablation and K-Ras activation led to the development of ovarian, peritoneal and metastatic tumor masses. In the model, dendritic cell depletion early in the disease led to greater tumor volume and depletion of the cells at advanced stages led to lower tumor volume than no depletion. The researchers are in ongoing discussions with an undisclosed pharmaceutical company to evaluate potential combination treatments with the model.</p> <p>SciBX 5(9); doi:10.1038/scibx.2012.237 Published online March 1, 2012</p>	Unpatented; unavailable for licensing	<p>Scarlett, U.K. <i>et al. J. Exp. Med.</i>; published online Feb. 20, 2012; doi:10.1084/jem.20111413 Contact: Jose R. Conejo-Garcia, The Wistar Institute, Philadelphia, Pa. e-mail: jrconejo@wistar.org</p>
Mouse model of Epstein-Barr virus (EBV)-driven B cell lymphoma	<p>Mice that express EBV latent membrane protein 1 (Lmp-1) in B cells could aid the development of new treatments for EBV-associated lymphoma. In the mice, T cell depletion led to the formation of Lmp-1⁺ tumors including diffuse large B cell lymphoma. In immunodeficient mice injected with Lmp-1⁺ tumor cells derived from the model, a fusion protein containing the extracellular domain of killer cell lectin-like receptor subfamily K member 1 (Klrk1; Cd314; Nkg2d) and an Fc fragment of mouse IgG2a decreased tumor growth compared with control protein. Preclinical studies to evaluate the Nkg2d-Fc fusion protein are ongoing.</p> <p>SciBX 5(9); doi:10.1038/scibx.2012.238 Published online March 1, 2012</p>	Patent application filed covering fusion protein; licensing information available from the Dana-Farber Cancer Institute Office of Research and Technology Ventures	<p>Zhang, B. <i>et al. Cell</i>; published online Feb. 17, 2012; doi:10.1016/j.cell.2011.12.031 Contact: Klaus Rajewsky, University of Cologne, Cologne, Germany e-mail: klaus.rajewsky@mdc-berlin.de</p>

This week in techniques (continued)

Approach	Summary	Licensing status	Publication and contact information
Mouse model of serous ovarian cancer	<p>A mouse model of high-grade serous ovarian cancer could help identify biomarkers or therapeutics to treat the disease. Female mice with conditional double knockout of <i>dicer 1 ribonuclease type III (Dicer1)</i> and <i>Pten (Mmac1; Tep1)</i> in the reproductive tract developed fallopian tube tumors. The tumors spread to the ovaries and metastasized to the abdominal cavity, killing all mice in 13 months. The disease that developed in the model resembled the human disease and suggests human serous ovarian cancer originates in the fallopian tubes. Next steps could include using the model to screen for therapeutics and to identify biomarkers for early detection.</p> <p>SciBX 5(9); doi:10.1038/scibx.2012.239 Published online March 1, 2012</p>	Patent and licensing status unavailable	<p>Kim, J. <i>et al. Proc. Natl. Acad. Sci. USA</i>; published online Feb. 13, 2012; doi:10.1073/pnas.1117135109 Contact: Martin M. Matzuk, Baylor College of Medicine, Houston, Texas e-mail: mmatzuk@bcm.tmc.edu</p>
Drug platforms			
Chemical and structural profiling of poly(ADP-ribose) polymerase (PARP) inhibitor selectivity	<p>Chemical and structural profiling of PARP inhibitors could help identify strategies for designing more selective inhibitors. <i>In vitro</i> studies determined the binding of 185 compounds, including clinical-stage PARP inhibitors, to purified catalytic domains from 13 of the 17 human PARPs. All of the clinical compounds and most of the other compounds bound to multiple PARPs. Next steps include developing selective inhibitors for several PARP family members.</p> <p>At least eight companies have PARP inhibitors in clinical trials for neurological indications or cancer.</p> <p>SciBX 5(9); doi:10.1038/scibx.2012.240 Published online March 1, 2012</p>	Unpatented; licensing status not applicable	<p>Wahlberg, E. <i>et al. Nat. Biotechnol.</i>; published online Feb. 19, 2012; doi:10.1038/nbt.2121 Contact: Herwig Schüler, Karolinska Institute, Stockholm, Sweden e-mail: herwig.schuler@ki.se</p>
Crystal structures to guide the design of immunoproteasome-specific inhibitors	<p>Crystal structures of constitutive proteasomes and immunoproteasomes could guide the design of immunoproteasome-specific inhibitors. Constitutive proteasomes and immunoproteasomes are variants of the proteasome, and the latter are associated with cancer, inflammation and autoimmune diseases. Crystal structures were solved for murine constitutive proteasomes and immunoproteasomes with and without the immunoproteasome-selective inhibitor ONX-0914 (PR-957). Next steps could include using the structural insights to design more potent and selective immunoproteasome inhibitors.</p> <p>Onyx Pharmaceuticals Inc.'s ONX-0914 is in preclinical development for autoimmune diseases.</p> <p>SciBX 5(9); doi:10.1038/scibx.2012.241 Published online March 1, 2012</p>	Unpatented; licensing status unavailable for	<p>Huber, E.M. <i>et al. Cell</i>; published online Feb. 17, 2012; doi:10.1016/j.cell.2011.12.030 Contact: Michael Groll, Technical University Munich, Munich, Germany e-mail: michael.groll@ch.tum.de Contact: Marcus Groettrup, University of Konstanz, Konstanz, Germany e-mail: marcus.groettrup@uni-konstanz.de</p>
Markers			
Phosphorylated α -synuclein (SNCA) as a marker for diagnosing and monitoring progression in Parkinson's disease (PD)	<p>Patient sample studies suggest measuring phosphorylated SNCA levels could help diagnose and monitor PD. In cerebrospinal fluid (CSF) samples, phosphorylated SNCA levels were higher in patients with PD than in healthy controls. Phosphorylated SNCA levels also were associated with PD severity in the patients ($p < 0.05$). Next steps include validating the findings in an independent patient population.</p> <p>SciBX 5(9); doi:10.1038/scibx.2012.242 Published online March 1, 2012</p>	Unpatented; licensing status not applicable	<p>Wang, Y. <i>et al. Sci. Transl. Med.</i>; published online Feb. 15, 2012; doi:10.1126/scitranslmed.3002566 Contact: Jing Zhang, University of Washington School of Medicine, Seattle, Wash. e-mail: zhangj@uw.edu</p>

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